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A Working Plan For Research on Persian Gulf Veterans' Illnesses

Persian Gulf Veterans Coordinating Board

First Revision

November 1996

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PREFACE

Persian Gulf War veterans report a variety of symptoms and illnesses that may have been caused by their military service. Although the Departments of Veterans Affairs (VA) and Defense (DoD) have taken important steps to ensure that these veterans have access to quality medical care, there is an urgent need to increase understanding of the nature and extent of these illnesses, and their potential connection to service in the Persian Gulf.

The overwhelming majority of Persian Gulf veterans who have come to VA or DoD for medical care have been found to have common conditions and have received appropriate treatment for their problems. However, similar to the general civilian population, some veterans have symptoms that are difficult to explain using current diagnostic criteria for illnesses. A critical unresolved issue is whether they are experiencing these symptoms at a higher rate than comparable non-Persian Gulf war veterans. In addition, many veterans have questioned whether the illnesses that are common and diagnosable are etiologically linked to their service in the Persian Gulf conflict. While many medical questions have been answered with existing knowledge of the Persian Gulf veterans' experience, others require scientific research.

The VA, DoD, Department of Health and Human Services (HHS), and Environmental Protection Agency (EPA), through the Persian Gulf Veterans Coordinating Board (PGVCB), have led the way in the conduct of research on Persian Gulf veterans' illnesses. In 1995 it was apparent that the scope of the research issues necessitated the development of a working plan to help the Persian Gulf Veterans Coordinating Board coordinate federally-sponsored research in a way that all the relevant research issues would be targeted but unnecessary duplication would be avoided. This document is the first revision of the original 1995 *A Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1995). Because research, by its nature, often leads to unexpected findings, as well as refinement in thinking about specific topics, the original plan was designed to be flexible and evolve over time. New research findings in the past year and other information that has come to our attention, as well as the initiation of new research, have led to the need for a revision of the *Working Plan.* It is anticipated that the *Working Plan* will undergo further revisions in the future.

The original research plan and subsequent revisions attempt to balance the need for specific, targeted research directions, with the awareness that successful research, fostered by sound research questions, arises from the minds of independent scientists in research laboratories. Therefore, the *Working Plan* sets the broad research areas in which it is believed investment will most likely bring new and useful knowledge.

Although the *Working Plan* is primarily intended to guide federal decision makers in establishing research priorities, it is also meant to provide information to members of Congress, the scientific community, the public and, importantly, the veterans of the Persian Gulf conflict, about the manner in which the federal government is carrying out this important research.

In the interest of completeness, this revision of the *Working Plan* includes material from the original 1995 *Working Plan.* New research information is woven into the main body of this revised *Working Plan.*

It is important to note that the *Working Plan* is an essential component of research, and that research is only one element of a broader strategy aimed at addressing the health problems and concerns of Persian Gulf veterans and their families. These elements include:

- **MEDICAL CARE**
  Providing appropriate medical care has been a top priority of VA and DoD. The two departments have acted aggressively to ensure the delivery of high quality medical care to Persian Gulf veterans.

- **RESEARCH**
  Research, which is the subject of the present document, is indispensable to the improvement of medical care for Persian Gulf veterans, the institution of appropriate interventions, and to the formation of a firm basis for compensation.

- **COMPENSATION**
  VA and DoD continue to work diligently to ensure prompt and appropriate compensation of Persian Gulf veterans disabled by their military service.

- **EDUCATION AND OUTREACH**
  Persian Gulf veterans and their health care providers must have access to the latest information on medical care, compensation, and research. This information will enable veterans to make sound judgments about their own health status, and to know how and where they can seek assistance. It will also enable physicians, and other health care providers, to provide state-of-the art diagnoses and treatment to veterans.

Finally, to help ensure that the US Government is doing everything possible to determine the causes and provide care to those who are ill, the President established a Presidential Advisory Committee on Gulf War Veterans' Illnesses that began its work in August 1995. This Advisory Committee is reviewing and providing recommendations on the full range of US Government activities on this important issue. Its final report is expected in December, 1996.

Through the continued implementation of the *Working Plan*, in conjunction with the other components of the overall strategy, it is hoped that confident, reliable answers to the concerns of Persian Gulf veterans can be obtained as quickly as possible and with maximal efficiency.

Kenneth W. Kizer, M.D., M.P.H.
Under Secretary for Health
Department of Veterans Affairs

1. EXECUTIVE SUMMARY

Since veterans returning from the Persian Gulf first started to report symptoms and illnesses in late 1991, a significant number of clinical evaluation and research activities have been undertaken. In 1995 the magnitude of the research effort required implementation of a comprehensive plan. This resulted in publication by the Persian Gulf Veterans Coordinating Board (PGVCB) of *A Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1995) on August 5, 1995. Since that time the number of research programs investigating Persian Gulf veterans' illnesses has increased substantially. Some research programs have begun to produce results. New information about potential exposures to chemical weapons has become available. These changes in the context within which research is conducted have necessitated this revision of the 1995 *Working Plan*. As with the original document, the current plan maps out the course by which the following goals can be pursued:

- Establish the nature and prevalence of symptoms, diagnosable illnesses, and unexplained conditions among Persian Gulf veterans in comparison to appropriate control groups;

- Identify the possible risk factors for any illnesses, beyond those expected to occur, among Persian Gulf veterans;

- Identify appropriate diagnostic tools, treatment methods, and prevention strategies for any excess illness conditions found among Persian Gulf veterans.

The *Working Plan* is coordinated by the Department of Veterans Affairs (VA) in conjunction with the Persian Gulf Veterans Coordinating Board. The research conducted under the aegis of this plan is executed by various departments and agencies, inluding VA, DoD, and HHS. The Research Working Group (RWG) of the PGVCB is the primary research coordinator and is charged with assessing the state and direction of research; identifying gaps in factual knowledge and conceptual understanding; identifying testable hypotheses; recommending research directions for participating agencies; reviewing research concepts as they are developed; collecting and disseminating scientifically peer-reviewed research information; and ensuring that all research conducted under the umbrella of the RWG undergoes appropriate scientific peer-review, and that the results of peer-review lead to appropriate actions by the sponsoring agencies.

Establishment of the prevalence of symptoms and illnesses in comparison with appropriate control populations is an essential base upon which additional research depends. If Persian Gulf veterans are experiencing symptoms and illnesses that are in excess of expectations for such a population, further research into risk factors can then be approached by separating the overall investigation into two categories: analysis of health outcomes and analysis of exposures. These analyses need to be conducted in a manner that defines the association between exposures and outcomes.

Based on the findings of three scientific panels -- the Defense Science Board Task Force (DSB, 1994); the NIH Technology Assessment Workshop (NIH, 1994); and the Institute of Medicine (IOM, 1995) -- and other current information, exposures to psychological war

stressors, *Leishmania tropica* (*L. tropica*), petroleum products, insecticides and insect repellents [possibly in combination with pyridostigmine bromide (PB)], are important to consider if any excess illnesses are found. Vaccines, chemical agents resistant coating (CARC) paint, depleted uranium (DU) and smoke from oil well fires have been considered by the scientific panels as unlikely sources of Persian Gulf veterans' illnesses.

A key component of the 1995 *Working Plan* was an assessment of current knowledge and research on Persian Gulf veterans' illnesses. This assessment, along with guidance from the aforementioned scientific panels, led to the identification of the following areas of inquiry for which significant gaps in knowledge existed at that time:

- Information on the prevalence of symptoms, illnesses, and/or diseases within other coalition forces;
- Information on the prevalence of symptoms, illnesses, and/or diseases within indigenous populations within the Persian Gulf area including Saudi Arabia and Kuwait;
- Information on the prevalence of adverse reproductive outcomes among Persian Gulf veterans and their spouses;
- Simple and sensitive tests for *L. tropica* infection that could lead to quantification of the prevalence of *L. tropica* infection among Persian Gulf veterans; and
- Information on the long-term, cause-specific mortality among Persian Gulf veterans.

In June of 1995 DOD issued a Broad Agency Announcement (BAA) soliciting research proposals to investigate Persian Gulf veterans' illnesses. Proposals were sought from federal and non-federal scientists who were encouraged to broadly direct their efforts to epidemiology, clinical research, and research on pyridostigmine bromide. The solicitation was given additional focus by the research gaps identified in the 1995 *Working Plan.* In June 1996, DoD and VA announced the award of the first 12 of 15 new research grants as an outcome of the original BAA. These were selected on the basis of scientific merit by an independent scientific review panel, and on program relevancy derived from the list of research gaps. These new projects, and other research initiatives in 1995/1996, address most of the gaps identified in the 1995 *Working Plan.*

Events in 1995/1996, including the addition of new research, results of ongoing research, and new information about exposures during the Persian Gulf War, form the basis of a new assessment of knowledge and research.

In the 1995 *Working Plan* it was stated that lacking confirmatory evidence of exposure to chemical or biological weapons, research on chemical and biological weapons should not be undertaken. Since then, there have been reports of potential exposures resulting from allied bombing of two Iraqi chemical weapons facilities, and the destruction by US ground forces of a munitions bunker and storage pit that United Nations inspection teams have concluded contained sarin and cyclosarin. This new information raises concern about chemical weapons exposure, and leads to recommendations for more research on the long-term effects of low-level exposures to chemical agents, including basic research and epidemiologic investigations.

Epidemiologic studies are now beginning to provide information about the prevalence of self-reported symptoms, illnesses, and self-reported exposures among Persian Gulf veterans, and their spouses and children. Furthermore, clinical epidemiology and basic research are also beginning to yield results relevant to the determination of potential pathologies and their risk factors underlying the symptoms.

Findings from some of these studies indicate the following:

- Some groups of Persian Gulf veterans have self-reported an excess of symptoms in comparison with non-deployed veterans of the same era (Kaiser et al, 1995; CDC, 1995). A connection between symptoms and a specific disease pathology or pathologies has not been identified.
- Based on VA and DoD mortality studies to date (Kang and Bullman, 1996; Writer et al, 1996), there does not appear to be an excess of disease-specific deaths in Persian Gulf veterans when compared to veterans of the same era.
- A Navy study of hospitalizations (Gray and Coate, 1996a,b) indicates that, at least among active duty personnel, the rate of hospitalizations of Persian Gulf veterans does not exceed their non-deployed counterparts. This suggests that Persian Gulf veterans are not experiencing an excess of illnesses of a severity that would lead to hospitalization.
- One focused study of a small cohort of Persian Gulf veterans (Penman et al, 1996) and one study of military hospitalizations (Cowan et al, 1995) did not uncover an excess of birth defects among their offspring. Several ongoing and new epidemiologic studies are investigating pregnancy and birth outcomes. Results from these studies will begin to be available in 1997.
- A DoD study (US Army, 1995) of the interaction of PB, DEET, and permethrin in high dose, orally-exposed rats provides evidence in an animal model for synergistic effects of these compounds. Synergism is also suggested in a study of neurotoxicity in chickens at lower, though still acutely toxic, doses (Abou-Donia et al, 1996). This research suggests the need for further exploration of the potential interactive effects of these compounds at doses of greater relevance to humans. Research currently being conducted by DoD and VA will attempt to further address issues of PB and other compounds that could have interacted with it.
- A single study focusing on high-level central nervous system processing (Goldstein et al, 1996) found no clinically significant neuropsychological differences between a symptomatic, self-selected group of Persian Gulf veterans and a control group, with psychological stress accounting for the small deficits that were detected.
- A study focusing on the peripheral nervous system (Jamal et al, 1996) in 14 self-selected Persian Gulf veterans found small, but significant differences in 3 of 22 tests of peripheral nerve function related to large fiber peripheral nerve function and thinly myelinated small fiber function.

The epidemiologic investigations cited above were generally conducted in narrowly defined cohorts not necessarily representing the entire population of Persian Gulf veterans. Therefore, the ability to generalize beyond those studies to larger populations of Persian Gulf veterans is

limited. However, results from ongoing epidemiological studies, when completed and combined with these findings, will facilitate broader generalizations.

In addition to new research findings and new research initiatives in the United States, the US Government is coordinating its research effort with Great Britain and Canada, each of whom participated in the Persian Gulf War as coalition partners. VA scientists are also actively collaborating with researchers in Denmark and Japan. Denmark participated in the Persian Gulf War as a coalition partner. The collaboration with Japanese scientists involves follow-up research on individuals exposed to sarin in the Tokyo subway terrorist incident in 1995.

Emerging findings from ongoing research in the past year, and new factual information on the potential for chemical weapons exposure in southern Iraq in 1991 lead to the following specific, near-term recommendations for additional research:

- Follow-up of the mortality experience of Persian Gulf veterans, encompassing cause-specific mortality, at appropriate future time-points;
- More longitudinal follow-up studies of the health of Persian Gulf veterans, including those with illnesses that are difficult to diagnose;
- Critical peer-review of models used to predict exposure concentrations of environmental pollution (such as the Kuwait oil well fires) and chemical warfare agents (such as the demolition of weapons storage sites at Khamisiyah in March, 1991 and aerial bombing of chemical weapons facilities during the air war);
- Assessment of the potential for clinical investigations of the health status of the service members in the vicinity of Khamisiyah when weapons bunker 73 and the storage pit were detonated in March, 1991. If deemed possible, such clinical investigations should be carried out.

Additional research on health-related issues arising from the Persian Gulf experience but with potential for more general applicability to future conflicts is also recommended, including:

- Investigation of the risk factors for the development of stress-related disorders including, but not limited to, post-traumatic stress disorder (PTSD);
- Investigation of the risk factors responsible for the observed excess mortality due to external causes (e.g., motor vehicle accidents) in veterans of all wars and conflicts;
- Exploration of the development of practical, sensitive, and specific biomarkers of exposure to chemical agents, including organophosphate nerve agents and vesicants such as sulfur mustard.
- Toxicological and, where feasible, epidemiological research on the potential for long-term health effects resulting from low-level, sub-clinical exposures to chemical agents, particularly organophosphate agents such as sarin;
- Development of a strategic plan for research into the potential long-term health consequences of exposure to low-levels of chemical warfare agents;
- If a simple, sensitive and specific, as well as economic, test for *L. tropica* infection becomes available, seroepidemiologic studies may be undertaken in Persian Gulf veterans. Indeed, when feasible and practical, sera of veterans should be stored in expectation of the possibility for such studies. Despite the declining importance of *L.*

tropica as a risk factor in Persian Gulf veterans, continued research on tests for *L. tropica* infection are valuable for potential future deployments.

It is further recommended that a contextual framework for the results of completed and ongoing studies be provided to develop approaches for the collective interpretation of research results. A meeting of researchers should be organized to provide such a framework.

Because of the changing nature of scientific research, and the acquisition of new factual information, this plan will likely undergo additional revisions in the future.

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2. INTRODUCTION

2.1 BACKGROUND

A wide variety of symptoms and illnesses began to be reported by veterans returning from the Persian Gulf conflict in late 1991. The initial response to this problem appropriately involved descriptive studies including:

- Clinical evaluations;
- Disease outbreak and cluster investigations;
- Population health surveillance;
- Initial exposure inventory and assessment;
- Troop location.

The response included establishing the Department of Veterans Affairs (VA) Persian Gulf Registry Health Examination Program ("Persian Gulf Registry") and Persian Gulf Referral Centers, and the Department of Defense (DoD) Comprehensive Clinical Evaluation Program (CCEP). These major clinical undertakings resulted in appropriate medical care and allowed the systematic collection of clinical, and other descriptive data, regarding the health of Persian Gulf veterans that would aid in treatment of veterans and active duty service members.

As of October 1996, over 62,000 Persian Gulf veterans had completed the VA registry examination and had their examination. Of veterans in the registry with one or more symptoms, 77% received medical diagnoses from VA clinicians. The DoD CCEP reveals a similar pattern of findings among the more than 18,500 participants who had completed the examination as of the same time (DoD, 1996)

Overall, the VA Persian Gulf Registry and the CCEP have identified a wide spectrum of overlapping symptoms involving multiple organ systems. As of May 1996, the most commonly reported symptoms from the VA Persian Gulf Registry include:

SYMPTOM	FREQUENCY
Fatigue	20%
Skin rash	18%
Headache	18%
Muscle/Joint pain	17%
Memory loss	14%
Shortness of breath	8%
Sleep disturbances	6%
Diarrhea and other GI symptoms	5%
Chest Pain	4%

In the initial stages of the search for a cause of these symptomatic conditions, attention was brought to the multitude of environmental, occupational, and biological exposures that may have been experienced by many of the troops. When combined with the unique conditions of a rapid, large-scale deployment, it was evident that a quantitative understanding of the nature of these exposures would be needed along with better understanding of the illnesses.

2.2 THE ROLE OF RESEARCH

The need to establish whether there is a link between medical conditions and service in the Persian Gulf resulted in the initiation of a broad-based research program. The *Working Plan for* research is intended to help coordinate and focus the research efforts sponsored by the federal government in a coherent and cost-effective manner. This document presents an approach to answering questions about the nature of illnesses experienced by Persian Gulf veterans. This research is intended to pursue the following goals:

- Establish the nature and prevalence of symptoms, diagnosable diseases, and other conditions in Persian Gulf veterans in comparison to appropriate control populations;
- Identify possible risk factors for any excess morbidity or mortality among Persian Gulf veterans; and,
- Identify appropriate diagnostic tools, treatment methods, and prevention/intervention strategies for conditions found among Persian Gulf veterans.

The research necessary to achieve these goals includes basic research, which is necessary to establish the knowledge base upon which clinical and epidemiological research are built. Where appropriate and feasible, research will address family members of veterans, as well as veterans per se.

2.3 RESEARCH MANAGEMENT AND COORDINATION

Research on Persian Gulf veterans' illnesses is complex, involving a number of different approaches and outcomes. The federal research enterprise involves scientists conducting research sponsored by VA, DoD, and HHS. Each of these Departments have distinct, though complementary, capabilities and capacities for conducting and sponsoring research on Persian Gulf veterans health issues. Each Department has its own appropriation for extramural and intramural general biomedical research programs. Extramural funds generally support research efforts at non-federal institutions such as universities. Intramural funds generally support in-house research. However, at most VA medical centers, intramural research is conducted in conjunction with academic medical center affiliates. The Department of Defense also has a separate item in its appropriation for DoD/VA collaborative research on health problems shared by veterans and active duty service members alike.

The biomedical research programs in VA, DoD, and HHS have well established management structures for science policy formulation and the solicitation, scientific peer review, and funding of both extramural and intramural programs. The coordination and management of research on Persian Gulf veterans' illnesses has required the establishment of an overall research policy framework linking each Department's research management hierarchy. The linkage is provided through the Research Working Group of the Persian Gulf Veteran's Coordinating Board [composed of representatives from VA, DoD, HHS, and the Environmental Protection Agency (EPA)]. The Research Working Group is charged with assessing the state and direction

of research; identifying gaps in factual knowledge and conceptual understanding; identifying testable hypotheses; recommending research directions for participating agencies; reviewing research concepts as they are developed; collecting and disseminating scientifically peer-reviewed research information; insuring that the appropriate research is done without unnecessary duplication; and insuring that federally sponsored research undergoes appropriate peer review and oversight. As an operational policy, the Research Working Group works through the line management authority each department maintains over its intramural scientists, scientific program managers (responsible for extramural research), and their budgets.

Each Department engaged in research on Persian Gulf veterans' illnesses emphasizes the need for ongoing prospective and retrospective peer review of research. Because of the urgency of the health concerns of Persian Gulf veterans and their families, as well as the diverse nature of the reported illnesses, review and oversight of research is essential. VA, DoD and HHS have established several oversight mechanisms to capture the diverse nature of the overall effort; some oversight mechanisms are broad-based, encompassing all research issues, whereas others are more focused on individual research projects and programs.

2.4 PURPOSE OF THE WORKING PLAN

This plan:

- Identifies the knowledge needed to achieve the above-stated goals;
- Identifies the knowledge that is currently available or will be obtained from ongoing research at some time in the foreseeable future;
- Identifies the research areas that need to be covered to close the gap between what is known and what is needed.

This plan is a dynamic working document that will undergo periodic modifications as new knowledge emerges and as research findings improve the understanding of Persian Gulf veterans' illnesses. The current document is the first revision of the original 1995 *Working Plan* and replaces the original document.

2.5 ORGANIZATION OF THIS DOCUMENT

To establish a knowledge baseline for the *Working Plan*, it is valuable to first examine the assessments of Persian Gulf veterans' health issues carried out by various expert panels. These include the NIH Technology Assessment Conference on Persian Gulf Veterans Experience and Health, the National Academy of Science/Institute of Medicine/Medical Follow-Up Agency panel on the Health Consequences of Service During the Persian Gulf War, the Defense Science Board Task Force on Gulf War Health Effects, and the Presidential Advisory Committee on Gulf War Veterans' Illnesses. Section 3 provides a brief overview of the assessments conducted by these panels. In the period since reports from the aforementioned panels were published there have been research findings that must be integrated with previous assessments. Section 4 is an assessment of research needs factoring in prior assessments, contemporary research findings, and the current research portfolio. Recommendations for additional research resulting from this assessment include research that is specific to the health

experience of Persian Gulf veterans, as well as research that has long-term impact for future deployments and military conflicts.

The Persian Gulf Veterans' Illnesses Research Database is provided for reference in the Appendix. To the best of our knowledge, it contains all relevant and credible research on Persian Gulf veterans' illnesses sponsored by the federal government and, along with research information from the non-federal research sector, is the basis for the determination of future research directions. It also includes 15 new research projects awarded by DoD as a result of a Broad Agency Announcement (BAA) in 1995 soliciting research from federal and non-federal investigators. The selection of research projects was based on scientific merit and program relevancy. Program relevancy was determined in part by the research gaps identified in the 1995 *Working* Plan. A more detailed summary of federally sponsored research in 1995 can be found in the *Annual Report to Congress: Federally Sponsored Research on Persian Gulf Veterans' Illnesses, 1995* (PGVCB, 1996a)

3. GENERAL FINDINGS FROM PANEL ASSESSMENTS

In late 1993, as information from initial descriptive studies became available and plans for future studies were being developed, it was evident that an assessment of the data and investigational activities was in order. Assessment activities were undertaken by the Defense Science Board (DSB), the National Institutes of Health (NIH), the National Academy of Sciences/Institute of Medicine/Medical Follow-up Agency (IOM), and most recently by the Presidential Advisory Committee on Gulf War Veterans' Illnesses.

3.1 DEFENSE SCIENCE BOARD

DoD commissioned the Defense Science Board Task Force on Gulf War Health Effects. The Task Force was specifically charged with reviewing all available intelligence and reports of detection of chemical agents and toxins during Operations Desert Shield/Desert Storm (ODS/DS) and the post-conflict period. In addition, the Task Force was to review scientific and medical evidence relating the possibility of low-level exposure to chemical and biological warfare (CBW) agents to potential long term health effects. A similar review was conducted for possible industrial pollutants and other potential causes of unexplained illnesses. The DSB Task Force met six times between November 1993, and March 1994. In the course of its work, the Task Force heard presentations from a wide range of scientific and medical experts from within and outside DoD. The Task Force published its final report in June 1994 (DSB, 1994). The members of the DSB Task Force reached consensus on a number of key points, including:

1. There is "... no scientific or medical evidence that either chemical or biological warfare was deployed at any level against us, nor that there were any exposures of US service members to chemical or biological warfare agents in Kuwait or Saudi Arabia."

2. There is "...no persuasive evidence that any of the proposed etiologies caused chronic illness on a significant scale in the absence of acute injury at initial exposure."

3. There is insufficient epidemiological evidence at this time "...to support the concept of any coherent 'syndrome'."

Because many veterans report symptoms similar to Chronic Fatigue Syndrome (CFS), the DSB Task Force felt it would be advantageous to coordinate further research on veterans' illness in this category with ongoing studies of CFS in the civilian population.

In light of new knowledge indicating there may have been release of chemical warfare agents in March, 1991 as a result of demolitions of weapons bunkers near Khamisiyah, Iraq (see Section 4.1.5), the first point is drawn into question. However, there is still no direct scientific or medical evidence of exposure.

3.2 NIH TECHNOLOGY ASSESSMENT WORKSHOP

The NIH Technology Assessment Workshop, "Persian Gulf Experience and Health", was convened April 27-29, 1994, and was co-sponsored by VA, DoD, HHS, and the Environmental Protection Agency (EPA). The expert panel addressed four issues: (1) the prevalence of unexplained illnesses; (2) whether a case definition could be developed; (3) potential etiologies of unexplained illnesses; and (4) recommendations for future research.

The NIH panel found that insufficient epidemiological data existed to determine whether there was an increased prevalence of illnesses among veterans due to service in the Persian Gulf War (NIH, 1994). The panel also concluded that while there are several complexes or patterns of symptoms unexplained by established disease categories, it would be premature to establish a case definition. The panel could not identify a single or multiple etiology for unexplained illnesses, but noted the appearance in some Persian Gulf veterans of a newly identified form of leishmaniasis (viscerotropic leishmaniasis). The panel also suggested that the unique stresses of the Persian Gulf experience may have led to a previously unrecognized manifestation of post-traumatic stress disorder (PTSD).

3.3 NATIONAL ACADEMY OF SCIENCES/INSTITUTE OF MEDICINE/ MEDICAL FOLLOW-UP AGENCY

As directed by P.L. 102-585, VA and DoD entered into a contract with the National Academy of Sciences/Institute of Medicine/Medical Follow-up Agency (IOM) to "...review existing scientific, medical, and other information on the health consequences of military service in the Persian Gulf theater of operations during the Persian Gulf War." In contrast to the NIH Workshop, this effort was designed to conduct an assessment in greater depth, over a three year time period.

On January 4, 1995, the IOM issued a report "Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Action" (IOM, 1995). In general the IOM panel endorsed the DSB and NIH findings of no single disease entity with no single etiology. The panel also strongly emphasized the importance of population-based studies. The panel found no evidence that either chemical or biological warfare (CBW) agents were used against coalition troops during the Persian Gulf conflict and, as a consequence, recommended that this not be a factor in considerations of the causes of Persian Gulf veterans' illnesses.

The IOM panel completed its deliberations in the Summer of 1996 and issued its final report in September, 1996 (IOM, 1996). In this report (which stands as a separate document from the January, 1995 report) the panel stated that it could find no scientific evidence to date demonstrating adverse health consequences associated with service in the Persian Gulf War beyond the few documented cases of leishmaniasis, combat-related or injury-related mortality or morbidity, and increased risk of psychiatric sequelae of deployment. The panel went on to state that there is a strong likelihood that no single hypothesis could account for all of these, whether or not the illnesses result from service in the Persian Gulf War. Finally, the panel observed that after previous wars and conflicts, a proportion of military service personnel and veterans have had medical complaints of varying degrees of severity that are not explainable based on identifiable health hazards or physical illnesses. This observation echoes work by Hyams et al (1996) tracing such a phenomenon back at least to the Civil War.

3.4 PRESIDENTIAL ADVISORY COMMITTEE ON GULF WAR VETERANS' ILLNESSES (PAC)

The President established this advisory committee by Executive Order on May 26, 1995. The 12 member committee is composed of scientists, health care professionals, veterans, and policy experts. The Committee is charged with reviewing and providing recommendations on the full range of government activities relating to Persian Gulf veterans' illnesses.

The Committee released an interim report in February 1996 (PAC, 1996a). Although the Interim Report stated that VA, DoD, and HHS research programs are generally well designed and should lead to answers, it also had several recommendations. The Committee's recommendations covered issues such as peer review, coordination of agency research activities, the use of public advisory committees and the availability of information on troop exposure. In response to the Interim Report, the agencies developed a coordinated plan of action (PGVCB, 1996b) that responds to the Advisory Committee's interim recommendations. The final report of the Committee is scheduled for release in December, 1996.

The Committee made no findings about specific illnesses or exposures in the Interim Report. However, at a public meeting of the PAC in Chicago, Illinois, on July 8-9, 1996 (PAC, 1996b), Committee Staff presented to the Committee their assessment of major potential risk factors. A meeting in Cincinnati, Ohio, on July 23, 1996 (PAC, 1996c) was devoted specifically to stress as a risk factor, and a meeting in Denver, Colorado, on August 6, 1996 (PAC, 1996d) revisited depleted uranium and oil well fires as risk factors. As in the IOM Final Report (IOM, 1996), Committee Staff were unable to identify any single risk factor, other than stress, that could explain a large number of illnesses reported by Persian Gulf veterans. It should be emphasized that these conclusions were those of Committee Staff and do not necessarily represent the final findings of the Committee proper.

As will be seen from the discussion of various exposures and health outcomes in the next section, the views of the Persian Gulf Veterans Coordinating Board Research Working Group do not diverge from those of the various review and assessment panels. As new information has become available, however, we continue to build on these reviews and assessments. Nevertheless, the door must not be closed to considerations of other exposures and outcomes since new research findings from ongoing studies have the potential for affecting these conclusions.

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4. FRAMING THE PROBLEM

In the 1995 *Working Plan* a set of research questions were developed based on the NIH, DSB, and IOM (in the initial report of January, 1995) findings and recommendations. Each question was followed by an evaluation of the degree to which then current research was addressing these questions, followed by a set of recommendations for additional research. In this revised version the formulation of these questions is restated. Current, on-going (or recently completed) research projects addressing these questions are then presented along with relevant findings. This is followed by an updated list of research needs for the question of concern.

As with the 1995 *Working Plan*, the most important question about the health of Persian Gulf veterans is:

Are Persian Gulf veterans experiencing a greater prevalence of symptoms and illnesses in comparison with an appropriate control population?

From the answer to this question springs virtually all subsequent questions that may be addressed through research. For example, if there is an increased prevalence of certain symptoms among Persian Gulf veterans in comparison to controls, then what disease or diseases are being manifested by these symptoms, and what connection with service in the Persian Gulf might exist? Therefore, the first research question that needs addressing is:

RESEARCH QUESTION 1

What is the prevalence of symptoms/illnesses in the Persian Gulf veterans population? How does this prevalence compare to that in an appropriate control group?

In the past year two studies (CDC, 1995; Kaiser et al, 1995) have demonstrated that while objective measures remained consistent between study and comparison groups, in select cohorts of Persian Gulf veterans there is a greater prevalence of symptoms (similar in type to the VA Persian Gulf Registry and the DoD CCEP) when compared to non-deployed veterans. Because of the limited sizes of these cohorts generalizability is difficult. In addition, Coate et al (1995) have shown that active duty service members who served in the Persian Gulf had no more hospital admissions than those who were not deployed to the Persian Gulf. This suggests that as a group Persian Gulf veterans are not experiencing a greater prevalence of major illnesses.

Research Underway

PROJECTS VA-2, 4, 5, 6, 18; DoD-1A,B,E,F, 30, 39; HHS-1, 2 (NOTE: Project numbers associated with current research refer to projects contained in the Appendix.): Components of each of these projects are designed to estimate the prevalence of symptoms in Persian Gulf veterans and compare this prevalence to control groups of non-deployed veterans.

Additional Research Needed

- The ongoing epidemiological studies will determine the need for additional studies.

If ongoing studies continue to demonstrate an increased prevalence of self-reported symptoms and illnesses, then the secondary questions regarding disease entity or entities must continue to be vigorously pursued.

Casting the problem of Persian Gulf veterans' illnesses into an exposure-outcome framework helps to isolate two interconnected questions: (1) what was the nature and extent of *possible exposures* experienced by veterans while in the Persian Gulf?, and (2) what adverse health outcomes, *if any*, have occurred among Persian Gulf veterans, beyond what would be normally expected in such a large population? These two questions lead to a third, namely: (3) is there a relationship, or set of relationships, between exposure to the complex environment of the Persian Gulf War theater and any *excess* health outcomes that is consistent with established biological and toxicological principles, and with epidemiological data? This last question requires identification and quantitation of both exposures and health outcomes. Investigation of exposures can lead to hypotheses about expected health outcomes based on the nature and extent of the exposures, and investigations of health outcomes can lead to hypotheses about exposures.

Because of the inherent logical value of separating the problem into exposure and health outcome, the *Working Plan* separates research oriented primarily toward exposure from research directed primarily at evaluating health outcomes.

4.1 EXPOSURES

While deployed in the Persian Gulf theater, troops may have experienced a variety of exposures, both natural and environmental/occupational in origin, to a varied extent. Potential exposures of concern that have been cited are: infectious agents (such as *Leishmania tropica*); smoke from oil well fires; exposure to other petroleum products and their combustion products; other occupational exposures such as pesticides, chemical agents resistant coating (CARC) paint; CBW agents; vaccines; pyridostigmine bromide (PB); and psychophysiological stressors of war. The number of troops and the amount of exposure to any one, or combination of, these exposures is not known at this time.

TABLE 2
Summary of Potential Exposures of Concern for Health Outcomes

Exposures	Scientific Review Panel DSB	NIH	IOM
Infectious Agents	+	+	+
Smoke from Oil Well Fires/Oil Spills	-	-	-
Other Petroleum Products	*	+	+
Other Occupational Exposures	*	+	*
CBW Agents	-	*	-
Vaccines	-	-	+
Pyridostigmine	*	+	+
War Stressors	+	+	+

\+ Recommended for further review and research

\- Unlikely to be of primary concern for long-term health consequences

* The exposure was either considered by the panel, but not highlighted, or was not considered by the panel.

Table 2 summarizes the findings of the DSB, NIH, and IOM panels with respect to these exposures. All three panels agreed that psychophysiological stressors of war and infectious agents required further review or research. Further research into exposure to other petroleum products and pyridostigmine bromide was recommended by IOM and NIH, but DSB made no specific recommendation. All three panels also agreed that it is unlikely that oil well fires or vaccines caused illnesses in Persian Gulf veterans.

With respect to CBW exposure, the NIH panel initially deferred making a finding about CBW until the DSB completed its deliberations. Both the DSB and the IOM (in its January, 1995 initial report) subsequently reported lack of confirmation of exposure to CBW agents. Further research related to these potential exposures was not recommended by DSB or IOM in its initial report (IOM, 1995). Recent findings that exposure of US service members to chemical warfare agents may have occurred near Khamisiyah, Iraq in March, 1991 have significantly altered this view (see Section 4.1.5 below).

Below is a discussion of each of the exposures. For each exposure a general background is provided along with any new research data that have become available. This is followed by specific research questions with statements of current research and any additional studies that are needed. Studies that pace other studies (i.e., studies that must be complete before others can proceed) or studies that are paced by other studies are identified.

4.1.1 Infectious Agents

Coalition troops were exposed to a number of infectious agents present in the Persian Gulf area. The most notable of these is the parasite *Leishmania tropica*. To date only 12 cases of viscerotropic and 20 cases of cutaneous leishmaniasis have been diagnosed among Persian Gulf veterans (DoD, 1996), clearly suggesting minimal exposure. Diagnosis of viscerotropic leishmaniasis, however, is difficult because there is no accurate serological test for the presence of the parasite. Thus, actual exposure and infection rates are difficult to obtain. After the passage of five years and the absence of a significant number of cases of either cutaneous or viscerotropic leishmaniasis, the likelihood of *L. tropica* as an important risk factor for widely reported illnesses has diminished.

Other infectious agents were also present in the Persian Gulf area that could cause chronic diseases, including schistosomiasis, Q fever and brucellosis (DeFraites et al. 1992; Ferrante MA et al. 1993). Only a few cases of these diseases have been diagnosed among the US troops who served in the Persian Gulf, and there is no indication that such infections are widespread or are related to unexplained illnesses (Hyams et al. 1995).

Acute infectious disease outcomes typical of cramped military living conditions, such as dysentery and respiratory tract infection, were actually lower than expected during the Persian Gulf conflict (DSB, 1994; Richards et al. 1993a,b; Richards et al. 1991). Exposure to other infectious agents such as mycoplasmas, bacteria, viruses, and fungi probably occurred but there is not a strong case from any clinical evaluations that supports these organisms as possible etiologic factors. However, because of the possible role for Leishmania in unexplained illnesses, all three scientific review panels recommended further research to develop a simple, sensitive and specific diagnostic test.

> **RESEARCH QUESTION 2**
>
> **What was the overall exposure of troops to *Leishmania tropica*?**

If this question is to be ultimately addressed, a highly sensitive, yet specific diagnostic screening test must be developed. Only then would it be possible to address the research question. Progress has been reported by Dillon et al (1994) who have developed a recombinant antigen that has been characterized and detects immune response in patients with viscerotropic leishmaniasis. Specificity and sensitivity of this test are currently unknown. Because of the potential for development of specific and sensitive serological tests, serum samples collected as a part of population-based epidemiological studies of Persian Gulf veterans should be banked, when feasible and practical, to facilitate testing once an appropriate test is available.

Despite the diminishing likelihood of *L. tropica* as a risk factor, it is worthwhile to continue work in this area because it is relevant for future deployments.

Research Underway

PROJECT DoD-S.A.B. 38: These three projects involve development of a reliable skin test (screening for past infection) and serologic assay (testing for active infections).

Additional Research Needed

- Development and testing of diagnostic tests determine all further leishmaniasis research directed at this research question.

4.1.2 Smoke from Oil Well Fires and Oil Spills

The US Army Environmental Hygiene Agency has characterized the carcinogenic and non-carcinogenic risk from exposure to smoke from the Kuwait oil well fires (USAEHA, 1994). This risk assessment demonstrates minimal potential carcinogenic risk. The bulk of non-cancer risk is from volatile organic compounds, but this risk is judged to be low. These risk assessments, however, are only valid for personnel located at sites where environmental measurements were made. In DoD-18 an oil well plume model is being developed using monitoring data as input. The model output, when expressed in a format compatible with the military geographic information system (GIS) for troop unit location (PROJECT VA-3), should provide an approximation of the oil well plume exposure as a function of time for troop units. This model will prove to be very valuable for future spatial analyses requiring exposure information. DoD and VA need to ensure that this model has been adequately peer reviewed. Based on previous recommendations of review panels and the lack of any new information that alters the findings, further oil well smoke exposure research beyond the USAEHA model, and its application to risk assessment, is not being pursued at this time.

4.1.3 Other Petroleum Products

During the war, some troops may have been exposed to petroleum vapors, solvents and combustion products. Kerosene, diesel and leaded gasoline from local sources were sometimes used for heating, ground spraying to suppress sand dust, and incinerating both trash and human waste. As a result, some troops could have been exposed to benzene, toluene, ethylbenzene, xylene and other petroleum combustion products. Elevated levels of sulfur dioxide, nitrogen dioxide, nitric acid, acidic sulfates, carbon monoxide, lead, respirable particulates and other pollutants may be expected in tents using unvented heaters burning gasoline and diesel fuels. There were no measurements of any of these pollutants in tents. Concern that this type of exposure was high enough for significant health consequences prompted both the NIH and IOM panels to recommend a simulation of exposure in tents heated by diesel fuel with composition similar to that used in the Persian Gulf area. The IOM noted the presence of elevated blood lead levels derived from autopsy specimens from seven service members who died in the Persian Gulf theater may have been related to contamination from specimen storage containers (IOM, 1996). The pharmacokinetics of lead make meaningful follow-up difficult at best (Legett RW, 1993). In an ongoing clinical study, investigators have not found any evidence of current elevated blood lead levels among Persian Gulf veterans (Roswell, 1995).

RESEARCH QUESTION 3

What were the exposure concentrations to various petroleum products, and their combustion products, in typical usage during the Persian Gulf conflict?

In one attempt to address this question investigators at NIH (HHS-3), in conjunction with USAEHA, have measured urinary metabolites of polycyclic aromatic hydrocarbons (PAH), PAH-DNA adducts, and genetic polymorphisms in 62 soldiers in June 1991, prior to deployment to Kuwait, eight weeks into their deployment, and after their return to Germany from Kuwait in October 1991. Results indicate that soldiers may not have experienced significant exposures to PAHs associated with the incomplete combustion of petroleum while stationed in Kuwait.

Research Underway

PROJECT DoD-2, 34: A component of DoD-2 involves the simulation of exposures to petroleum and petroleum combustion products in enclosed spaces. DoD-34 involves direct simulations of exposures in tents characterizing the nature and concentrations of petroleum combustion products.

PROJECT DoD-19: This research attempts to expand the modeling of DoD-18 to characterize all potential exposures in Kuwait and Saudi Arabia.

Additional Research Needed

- DoD and VA need to ensure that this and other exposure models have been adequately peer reviewed.

4.1.4 Other Occupational Exposures

Other potential environmental hazards, including pesticides, microwaves, chemical agent resistant coating (CARC) paint fumes, depleted uranium (DU) and cleaning solvents were present in the Persian Gulf theater. Some of these chemicals, such as CARC paint and DU, are not likely to be a primary cause of unexplained illnesses among Persian Gulf veterans because only small numbers of troops were exposed (NIH, 1994). A full assessment of risk from exposure to these chemicals cannot be made in the absence of accurate exposure data.

RESEARCH QUESTION 4

What was the extent of exposure to specific occupational/environmental hazards known to be common in the Persian Gulf veteran's experience? Was this exposure different from that of an appropriate control group?

Research Underway

PROJECT DoD-2: In addition to the petroleum and combustion products simulations listed above, simulations of exposure to other chemicals will also be conducted.

PROJECT DoD-19: This research attempts to expand the risk assessment modeling of DoD-18 to characterize all potential exposures in Kuwait and Saudi Arabia.

PROJECTS VA-2, 4A, 5A, 6-Core, 13; DoD-1A,D,E, 30, 39; HHS-1,2: Components of each of these epidemiology studies will collect self-reported exposure data using a variety of survey instruments. Results of exposure simulations may help to estimate the level of self-reported exposures.

Additional Research Needed

- The ongoing studies will determine the need for additional studies.

4.1.5 Chemical and Biological Warfare Agents

Both the DSB and IOM panels concluded that reports of the possible use of CBW agents cannot be confirmed and that bombing of Iraqi storage areas did not cause CBW agent exposure. While awaiting assessment of the DSB, the NIH panel drew no conclusions about the presence or absence of CBW. The IOM panel in their initial report (IOM, 1995) stated that claims of exposure to chemical or biological warfare agents should not be made or given credence in the absence of reliable substantiating data. Despite this, the DoD established the Persian Gulf Investigations Team (PGIT) to investigate, among other things, reports of CBW exposure provided to a 1-800 hotline.

In June 1996, DoD announced that a munitions bunker (#73) in Khamisiyah, Iraq, destroyed by US demolition teams on March 4, 1991, probably contained the chemical agents sarin and cyclosarin. On March 10 a pit containing sarin was also destroyed by US troops. Because of this, it is likely that some US military personnel in the vicinity were exposed to chemical warfare agents. In addition, chemical weapons storage sites at Muhammadiyat, and Al Muthanna, Iraq (northwest of Baghdad), were destroyed by allied bombing at the beginning of the Persian Gulf War, creating a potential risk of chemical agent exposure downwind of these sites.

Testimony provided to the Presidential Advisory Committee meeting on June 8-9, 1996, (PAC, 1996b) by representatives of the United Nations Commission charged with the accounting and destruction of weapons of mass destruction in Iraq, and by the US Central Intelligence

Agency (CIA), suggest that Khamisiyah was the only site in southern Iraq and Kuwait at which chemical weapons were present. If this is so, the incident at Khamisiyah may be entirely isolated. However, the report itself raises a sufficient degree of uncertainty to conclude that potential exposures to chemical warfare agents should no longer be excluded from consideration as a valid subject of research .

Two exposure issues immediately arise. The first one relates to the potential exposure of troops present at the Khamisiyah site at the time of demolition, and the potential exposure of troops as a result of the bombing of the Muhammadiyat and Al Muthanna weapons depots. The second relates to the more general issue of chemical agent exposure.

RESEARCH QUESTION 5

What were the potential exposures of troops to organophosphate nerve agent and/or sulfur mustard as a result of allied bombing at Muhammadiyat and Al Muthanna, or the demolition of a weapons bunker at Khamisiyah

In testimony at the June 8-9, 1996, PAC meeting (PAC, 1996b), contractors to the CIA presented the results of model calculations predicting ground level concentration of chemical agent as a function of distance and direction away from the March 4 detonation site at Khamisiyah (CIA, 1996). The model predicts that at the location of the troops chemical agent concentration should have been below any level expected to produce even mild acute effects. The CIA also modeled the plumes resulting from the bombings at Muhammadiyat and Al Muthanna. The model predicts levels well below what would be expected to cause even mild acute effects for troops located 400 - 500 km south of the sites. At the time of this writing, CIA has not completed its model calculations for ground level sarin concentrations resulting from the March 10 pit detonation. At the moment, model predictions provide some reassurance. However, model applications to these situations need to undergo scrutiny by outside experts.

Many of the ongoing epidemiological investigations collect self-reports on chemical agent exposure. Although these data may have value in assessing risk factors, the potential for report bias is always present. In the absence of actual exposure data acquired at the site of detonation, only model calculations can presently be relied upon. Exposure biomarkers for chemical agents have the potential for determining exposure on an individual basis after an actual exposure has ceased. However, there are no known exposure biomarkers for either organophosphate nerve agents or vesicants, and even if there were they would probably be of little value since over five years have elapsed since the Persian Gulf War.

Research Underway

PROJECTS VA-2, 4A, 5A, 6-Core, 13; DoD-1A,D,E, 30, 39; HHS-1,2: Components of each of these epidemiology studies are collecting self-reported exposure data using a variety of survey instruments. Although these studies are not directly focused on troops present at Khamisiyah, self-reporting and input from the troop unit locator database may provide some information on potential exposure, albeit not necessarily more detailed than

time and location of individual units. Results of further exposure simulations may help to estimate the intensity of self-reported exposures.

Additional Research Needed

- Existing plume model calculations should be critically reviewed.
- Exploration of the development of practical, sensitive, and specific biomarkers of exposure to chemical agents including organophosphate nerve agents and vesicants such as sulfur mustard.

The second exposure question can be stated as:

RESEARCH QUESTION 6

What was the extent of exposure to chemical agent, other than at Khamisiyah, Iraq, in the Persian Gulf as a function of space and time?

Despite the evidence indicating the very low probability of widespread chemical warfare agent exposures in the Persian Gulf, concern has been elevated by the bombings of Muhammadiyat and Al Muthanna, and the event at Khamisiyah in March 1991. Consequently there is a need to evaluate the potential for exposure of troops to chemical agent at other times and locations. In the absence of quantitative data, virtually all exposure information will be derived from self-reports, and thus, subject to bias. Although exposure biomarkers are probably of little use in the context of any chemical warfare agent exposure in the Persian Gulf, the need for reliable objective exposure markers is evident.

Research Underway

PROJECTS VA-2, 4A, 5A, 6-Core, 13; DoD-1A,D,E, 30, 39; HHS-1,2: Components of each of these epidemiology studies are collecting self-reported exposure data using a variety of survey instruments.

Additional Research Needed

- Exploration of the development of practical, sensitive, and specific biomarkers of exposure to chemical agents, including organophosphate nerve agents and vesicants such as sulfur mustard.

With respect to biological warfare agents, there continues to be no evidence of use by Iraq, or exposure of troops during or after the Persian Gulf War. These determinations were confirmed by both UN and CIA officials at the July 1996 meeting of the PAC (PAC, 1996b). The absence of any reports of infection from anthrax or acute illnesses from botulinum toxin in the Persian Gulf theater lends further credence to this conclusion.

4.1.6 Vaccines

Troops who served in the Persian Gulf conflict were vaccinated without significant side-effects against common infectious diseases with vaccines frequently used in the general population. In addition, approximately 150,000 troops received at least one dose of anthrax vaccine and about 8,000 received at least one dose of botulinum toxoid. Both vaccines have been used for many years without adverse effects. All three review panels stated that no long-term adverse effects have been documented or would be expected. Further study of the potential adverse effects of vaccines in this population is not recommended by any of the three panels, nor is it endorsed in this plan.

4.1.7 Pyridostigmine Bromide

Pyridostigmine bromide (PB) is a cholinesterase (ChE) inhibitor that was supplied to troops for use as prophylaxis against exposure to nerve agents. PB was distributed to troops in blister packs of 21 tablets of 30 mg each. PB tablets were taken on order when it was believed a gas attack was imminent. The recommended dosage was one tablet every 8 hours. PB has been in use for decades (at much higher dosages) in the treatment of patients with myasthenia gravis. Short-term side effects are well known -- e.g., nausea, vomiting, diarrhea, abdominal cramps, increased salivation, miosis, headache and dizziness. There have been no documented long-term side effects of this drug. Exposure information is provided solely from self-report of veterans.

RESEARCH QUESTION 7

What was the prevalence of PB use among Persian Gulf troops?

Research Underway

PROJECTS VA-2, 4A, 5A, 6-Core; DoD-1A,D,E, 30, 39; HHS-1,2: Components of each of these epidemiological studies collects self-reported PB use data for Persian Gulf veterans using a variety of instruments.

Additional Research Needed

- The ongoing epidemiological studies will determine the need for additional studies.

4.1.8 Psychophysiological Stressors of War

Psychiatric morbidity among US troops deployed to the Persian Gulf area was predicted even though the war was of short duration, resulted in relatively low numbers of casualties, and positive support for the war prevailed at home. Persian Gulf veterans were exposed to many psychophysiological stressors besides direct combat, such as sudden mobilization for military service (especially among members of reserve and National Guard units), exposure to dramatic oil well fires, the constant threat of CBW agents, and fear of combat in general. A wide range of somatic and psychological responses could be expected from individuals deployed to the Persian Gulf area from stress associated with deployment (Wolfe et al, 1993; Ursano and Norwood,

1996). All three review panels recognized the possible role of psychophysiological stressors associated with deployment and the possibility of a psychophysiological response among Persian Gulf veterans. All three panels, and the Committee Staff of the PAC (PAC, 1996d), have encouraged further scientific research in this area.

RESEARCH QUESTION 8

What was the prevalence of various psychophysiological stressors among Persian Gulf veterans? Is the prevalence different from that of an appropriate comparison population?

Research Underway

PROJECTS VA-2, 4A, 5A, 6-Core, 7, 12; DoD-1A,D,E, 4, 5, 6A,B, 30, 39, 40; HHS-1, 2: Components of these studies are acquiring self-reported data on exposure to psychophysiological stressors among Persian Gulf veterans and appropriate control populations. DoD-30 and DoD-39 will add specific information about the stressors in female Persian Gulf veterans and in British Persian Gulf veterans respectively.

Additional Research Needed

- More research is needed on the role of a variety of stressors as risk factors for later development of stress-related disorders, including, but not limited to, PTSD.

4.1.9 Troop Locations

One of the most important variables in considering any exposure is determining the location in the Persian Gulf War theater of individual service members as a function of time. Information about troop location down to the individual service member was not recorded. However, unit diaries (where a unit consists of approximately 100 troops) were maintained on a daily basis for all units. Matches between units and individuals can be made. The US Army and Joint Services Environmental Support Staff Group (ESG) is currently in the process of computerizing troop unit locations (PROJECT VA-3). Computerized records were completed for the Air Force, Navy, and Marines at the end of 1995. Eighty percent of the records were completed for the Army at the end of 1995. The remaining records will be complete by late 1996. Because the results from this project are needed for several epidemiological investigations, this project is of vital importance.

4.2 HEALTH OUTCOMES

The most frequently cited health outcomes and concerns related to service in the Persian Gulf are:

- Non-specific symptoms/symptom complexes;
- Immune function abnormality/autoimmune disease;

- Reproductive health outcomes;
- Genitourinary disorders;
- Pulmonary function abnormality;
- Neuropsychological/neurological outcomes;
- Psychological/psychiatric outcomes;
- Infection;
- Cancer/neoplastic disease;
- Mortality outcomes.

Table 3 provides a summary of the DSB, NIH, and IOM findings on health outcomes. When the potential for long-term health consequences was considered, all panels agreed that further research into psychological outcomes, non-specific symptom complexes, and leishmaniasis was needed. In addition, the IOM and NIH panels recommended research on neurological and neuropsychological outcomes. The remaining potential health outcomes were each considered significant by only one panel. In such cases, though, the other two panels had no comment. This latter observation must be treated with caution since concern about some potential health outcomes have been raised only recently.

TABLE 3
Summary of Reported Health Outcomes

Health Outcomes	Scientific Review Panels		
	DSB	NIH	IOM
Non-specific Symptoms/ Symptom Complexes**	+	+	+
Immune Function Abnormality	*	*	*
Reproductive Health Outcomes	*	*	+
Genitourinary Disorders	*	*	+
Pulmonary Function Abnormality	*	+	*
Neuropsychological - Neurological Outcomes	*	+	+
Psychological/psychiatric Outcomes	+	+	+
Infection	+	+	+
Cancer/Neoplastic Disease	*	*	*
Mortality Outcomes	*	*	+

\+ Recommended for further review and research
\- Unlikely to be of primary concern for long-term health consequences
* The outcome was either considered by the panel, but not highlighted, or was not considered by the panel.
** Including Chronic Fatigue Syndrome (CFS), chemical sensitivities, and fibromyalgia

Below, each health outcome is considered individually. For each health outcome a general background is provided. This is followed by specific research questions with statements of current research and any additional studies that are needed.

4.2.1 Non-Specific Symptoms/Symptom Complexes

Within any population the size of the Persian Gulf veterans cohort (approximately 700,000 who served in Operations Desert Shield/Desert Storm), individuals will experience various health complaints and may become ill at some time. Some of these symptoms and illnesses may not be fully explained despite intensive clinical work-ups. On the other hand, it is possible that some of these symptoms may fall into unique complexes that can be categorized.

RESEARCH QUESTION 9

Are Persian Gulf veterans more likely than an appropriate comparison group to experience non-specific symptoms and symptom complexes?

Recently, investigators have demonstrated in 1498 Seabees (Construction Battalion personnel) an increase of symptoms among deployed versus non-deployed Seabees with no physical correlates (Kaiser et al, 1995). Investigators with the CDC and the State of Pennsylvania have also demonstrated an increase of symptoms within groups of deployed versus non-deployed Air National Guardsmen in Pennsylvania (CDC, 1995). Symptom patterns in the latter study bear a similarity to Chronic Fatigue Syndrome, however the severity of symptoms is milder than in Chronic Fatigue Syndrome.

Research Underway

PROJECTS VA-2, 4A, 5A, 6-Core, 18; DoD-1A,E, 30, 39, 40; HHS-1,2: Components of each of these studies are acquiring data on self-reported non-specific symptoms. Some (see below) are also investigating the presence of identifiable symptom complexes. DoD-30 and DoD-39 are collecting data in cohorts of women and British Persian Gulf veterans respectively. DoD-40 is not designed to address prevalence of illness, but is a longitudinal study of PTSD in Persian Gulf veterans.

PROJECT VA-2; HHS-2: These studies include a physical examination to validate the self-reported symptoms on a subset of the survey study population.

PROJECTS VA-4A, 4B, 5B, 5C, 6B; DoD-31, 32, 39; HHS-2: Components of these studies are directed specifically at hypotheses that unexplained illnesses are associated with symptom complexes identified as CFS, fibromyalgia, or other symptom-based syndromes. At a minimum they should provide information on the prevalence of these complexes.

Additional Research Needed

- Most of the ongoing epidemiological studies are cross-sectional in nature. There needs to be additional emphasis placed on longitudinal studies focusing on the health of Persian Gulf veterans.

4.2.2 Immune Function

Suggestions have been made that some Persian Gulf veterans have experienced an alteration in immune function or host defense. One hypothesis is that aromatic hydrocarbons, and other related compounds, may cause suppression of immune function through activation of the aromatic hydrocarbon receptor (AhR) on cell lymphocytes and, subsequently, induction of lymphocyte death, thereby suppressing immune function.

RESEARCH QUESTION 10

Do Persian Gulf veterans have a greater prevalence of altered immune function or host defense when compared with an appropriate control group?

Research Underway

PROJECTS VA-4A, 5A, 6-Core, 17; DoD-37, 48: Virtually all of these studies are collecting standard, clinical immune function data. VA-4A is conducting research on a model for the upregulation of the AhR. VA-5A is studying peripheral blood polymorphonuclear leukocytes for chemokine expression. VA-5A is also examining blood mononuclear cells for reactivation for EBV, CMV, herpes 6 and herpes 7. DoD-37 is investigating alterations of immune response in male and female rats following PB, DEET, and permethrin exposures, alone or in combination. This project is also conducting *in-vitro* investigations of the effects of exposure to these compounds on human lymphocyte immune response. DoD-48 is investigaing the frequency of chromosome 7 inversions in blood specimens of symptomatic and asymptomatic Persian Gulf veterans.

Additional Needed Studies

- The ongoing studies will determine the need for additional studies.

4.2.3 Reproductive Health Outcomes

Adverse pregnancy and birth outcomes associated with Persian Gulf area deployment have been a major concern among the Persian Gulf veterans. The IOM panel has recommended that reproductive outcomes be included among the health endpoints in surveillance programs and that population-based studies of these outcomes be conducted.

RESEARCH QUESTION 11

Is there a greater prevalence of birth defects in the offspring of Persian Gulf veterans than in an appropriate control population?

An investigation was conducted by the Mississippi Department of Health in collaboration with CDC of birth defects in children of Persian Gulf veterans from a Mississippi national guard unit (Penman, 1996). Birth defects were identified and the diagnoses verified. The results were compared to expected values. The number of birth defects was not higher than expected for that population although the study had inadequate statistical power to detect any differences in specific defects. Investigators at the Naval Health Research Center in San Diego have examined military hospital discharge records for births to spouses of deployed active duty service members and among deployed active duty women (Cowan et al, 1995). They found that when these women were compared to their non-deployed counterparts, no difference in birth defects between the two groups could be found. Data have been collected to determine the prevalence of Goldenhar Syndrome among infants of the same populations (Araneta, 1996).

Current Research

PROJECTS VA-2, DoD-1D,E, 30; HHS-1: Components of each of these epidemiological studies are identifying through survey questionnaires birth defects in offspring of Persian Gulf veterans and in those of appropriate controls.

PROJECT DoD-1G: This study will match Persian Gulf veterans and non-deployed era veterans with birth defects registries in 7 states to determine if the overall and diagnostic-specific prevalence of congenital abnormalities differs among Persian Gulf veterans, non-deployed era veterans and the general population.

PROJECT DoD-35: This is a feasibility study to determine if all children born to Persian Gulf veterans residing in California can be identified and if congenital anomalies in the first year of life can be identified.

Additional Research Needed

- The ongoing epidemiological studies will determine the need for future studies.

RESEARCH QUESTION 12

Have Persian Gulf veterans experienced lower reproductive success than an appropriate control population?

Research Underway

PROJECTS VA-2; DoD-1D,E,C, 30; HHS-1: Different components of each of these studies will investigate the prevalence of failure to conceive, miscarriage, spontaneous abortion, and stillbirth and compare the prevalence to that of an appropriate control population.

Additional Research Needed

- The ongoing epidemiological studies will determine the need for future studies.

4.2.4 Genitourinary Disorders

There have been individual reports of sexual dysfunction among Persian Gulf veterans, including infrequent reports of these phenomena in both the VA and DoD surveillance systems.

RESEARCH QUESTION 13

Is the prevalence of sexual dysfunction greater among Persian Gulf veterans than among an appropriate comparison population?

Research Underway

PROJECTS VA-2; DoD-1A, 1E, 30, 39; HHS-1: Components of these epidemiology studies will determine, through survey questionnaires, the prevalence of various manifestations of sexual dysfunction in Persian Gulf veterans (or in the veterans' partners) compared to that in an appropriate comparison population.

PROJECT DoD-44: This project will investigate immunologic mechanisms by which a women could develop an allergic reaction to her sexual partner's semen.

Additional Research Needed

- The ongoing epidemiological studies will determine the need for additional studies.

4.2.5 Pulmonary Function Abnormality

Some troops may have been exposed to potentially significant amounts of petroleum vapors, combustion products and sand dust. Depending on exposure concentration and absorbed dose, repeated and chronic exposure to these chemicals and substances could possibly result in

impairment of pulmonary function. The NIH panel recommended a retrospective cohort study to investigate pulmonary function related to petroleum combustion products.

RESEARCH QUESTION 14

Do Persian Gulf veterans report more pulmonary symptoms or diagnoses than persons in appropriate control populations?

DoD investigators have found that while active duty deployed Persian Gulf veterans from a Seabee unit self-reported more respiratory symptoms, their objective pulmonary function tests did not differ from a non-deployed control group (Kaiser et al, 1995).

Research Underway

PROJECTS VA-2, 4A, 5A, 6-Core; DoD-1A, 1E, 30, 39; HHS-1: Components of these studies are using surveys to ascertain the self-reported prevalence of pulmonary symptoms/diagnoses (e.g., asthma, bronchitis, etc.) among Persian Gulf veterans compared to an appropriate control population. Exposure-outcome relationships will be explored.

Additional Research Needed

- The ongoing epidemiological and other studies will determine what, if any, additional studies are required.

RESEARCH QUESTION 15

Do Persian Gulf veterans have a smaller baseline lung function in comparison to an appropriate control group? Do Persian Gulf veterans have a greater degree of non-specific airway reactivity in comparison to an appropriate control group?

Research Underway

PROJECTS VA-4D; DoD-1A, 39: These projects are conducting cohort studies to determine whether there are any differences in pulmonary function and, to a lesser extent, airways reactivity between Persian Gulf veterans and Persian Gulf era veterans. As mentioned previously, DoD investigators have found that although active duty deployed Persian Gulf veterans from a Seabee unit self-reported more respiratory symptoms, their objective pulmonary function tests did not differ from a non-deployed control group (Kaiser et al, 1995).

PROJECTS DoD-2, 3: Components of these projects involve exposures of laboratory animals to a variety of inhaled pollutants. Pathophysiologic effects that may provide information on potential human health outcomes will be studied.

Additional Research Needed

- The ongoing studies will determine the need for additional studies.

4.2.6 Neuropsychological and Neurological Outcomes

The subjective reports of generalized fatigue and cognitive impairment in Persian Gulf veterans enrolled in the VA and DoD registries suggest the possibility of a neuropsychological component to their health problems. The self-reported exposures of troops to chemicals with potential neurological effects (such as PB, many of the pesticides, the insect repellent DEET, the insecticide permethrin, and potentially organophosphate chemical weapons) also suggest that neurological and neuropsychological outcomes may be important.

The simultaneous or sequential administration of certain compounds (for example, PB and the insect repellent DEET) conceivably could interact to produce an additive or synergistic neurologic effect. However, previous research has indicated that PB does not persist in the body and, therefore, is unlikely to cause any long-term effects (Breyer-Pfaff et al, 1985). Furthermore, it is unlikely that significant simultaneous exposure to PB and insecticides/repellents occurred. PB was most likely used during Operation Desert Storm lasting from late January to late February 1991. Insecticides and repellents, however, were most likely used during the summer months when insects are a particular problem. During the winter insects generally are not a problem that would lead to significant personal application of insecticides and repellents.

With respect to PB alone, the IOM panel concluded that PB is a well-studied medication belonging to a class of drugs about which extensive knowledge exists and that PB could interact with other compounds to cause acute and short-term problems, but was unlikely to cause chronic effects.

The determination that chemical agents (sarin in particular) were present in a munitions depot destroyed by US troops in Khamisiya, Iraq, on March 4 and March 10, 1991 has raised the possibility of exposure to chemical agents of these troops. Allied bombing of chemical weapons storage sites in Muhammadiyat and Al Muthanna has also raised concerns. Thus far, model calculations (CIA, 1996) of plumes from these events predict potential troop exposures at levels that would not likely have caused any acute effects. However, model calculations of the March 10 detonation are not complete. Further assessments of risk at Khamisiyah await these results. Regardless of the outcomes of the exposure models, there is the underlying question of whether exposure to anticholinesterases, such as organophosphate pesticides and chemical agents, at low, sub-clinical levels can produce chronic effects.

The Armed Forces Epidemiology Board (AFEB) has provided a report to DoD (AFEB, 1996) on their assessment of the potential long-term effects resulting from sub-clinical exposures to chemical agents. The report concludes that the scientific literature provides no scientific evidence that acute sub-clinical exposures to either sarin or mustard can result in long-term health consequences. However, the report cites one study (Burchfield et al, 1976) which has shown in primates long-term alterations in electroencephalogram (EEG) following low-level sarin exposure. It was unclear in the paper, however, whether these low-level exposures resulted in any acute effects. Because of this the AFEB report recommends that further research (using primate models) on the long-term EEG effects of sub-clinical and clinical doses of sarin. The AFEB acknowledges in its report that the meaning of these EEG changes is uncertain.

In 1994, about 600 people in Matsumoto, Japan were poisoned with sarin by terrorists. Morita et al (1995) followed 264 people who had sought treatment. Despite frank, acute, and objectively measurable effects consistent with an acute sarin exposure, virtually all of these individuals recovered within three months with no apparent sequelae.

Despite such reassurances, there is still some uncertainty regarding long-term effects from very low, sub-clinical exposures to cholinesterase inhibitors. If there are persistent effects, it is likely they would be manifested in neuropsychological and neurological deficits.

RESEARCH QUESTION 16

Is there a greater prevalence of organic neuropsychological and neurological deficits in Persian Gulf veterans compared to appropriate control populations?

Early studies of neuropsychological and neurological outcome suggest that self-selected Persian Gulf veterans demonstrate subtle differences from controls. Goldstein et al (1996) found that Persian Gulf Registry participants may have small, clinically insignificant neuropsychological deficits which could be related to the presence of psychological comorbidity. A study by Jamal et al (1996) found that Persian Gulf veterans who self-report with symptoms shows evidence of small alterations in peripheral nervous system function. However, these findings are probably confounded by several biases, including that of selection.

A study has been conducted of the acute interactions of PB, DEET, and permethrin when administered orally to rats (US Army, 1995). The endpoint studied was lethality at very high doses. They found potential synergism of effect when PB was combined with DEET and permethrin. More recently, a study by Abou-Dohia et al (1996) indicates that at high, non-lethal doses, there are acute synergistic neurotoxic effects in a chicken model. The relevance of high dose acute toxicity studies to the potential for chronic effects from acute low-level exposures is unknown.

A pilot clinical program at the Birmingham, Alabama, VA Medical Center has conducted neuropsychological tests on veterans from the VA Persian Gulf Registry who self-report exposure to environmental hazards including chemical weapons. Preliminary evidence (Kotler-Cope et al, 1996) does not show any pattern to indicate a common, identifiable neuropathologic process.

Research Underway

PROJECTS VA-2, 4A, 5A, 6-Core; DoD-1A, 1E, 32, 40; HHS-1: Prevalence of symptoms associated with neuropsychological and neurological deficits will be estimated, compared to an appropriate control population, and assessed in relation to significant subgroups of the veteran population, including those self-reporting specific exposures. DoD-40 does not investigate prevalence but is a longitudinal study to examine the time course of neuropsychological function in veterans with PTSD.

PROJECTS VA-4A, 4B, 5, 6A, 9, 10, 11: Components of these projects administer specific neuropsychological and neurological tests to groups of Persian Gulf veterans and Persian Gulf era veterans.

PROJECT VA-4A, 4B: In addition to research focusing on Persian Gulf veterans, investigators at the Boston VAMC Environmental Hazards Research Center are collaborating with scientists at St. Luke's Hospital in Tokyo, Japan. They are studying the long-term consequences of sarin exposure in individuals hospitalized following the terrorist incident in the Tokyo subway in June 1995. This should provide additional insight into long-term consequences from low-level exposures. The Boston VAMC researchers are also collaborating with scientists in Denmark who are studying Danish Persian Gulf veterans.

PROJECTS DoD-7A: This project will utilize a rat model to investigate the potential effects of depleted uranium on the nervous system.

Additional Research Needed

- Epidemiological investigations (if feasible) of the health of Persian Gulf veterans present at the detonation of the weapons depot at Khamasiyah in March 1991;
- Epidemiological investigations (if feasible) of the long-term effects of acute exposure to low-levels of chemical warfare agents;
- Toxicological investigations of the potential for long-term effects resulting from low-level exposures to chemical agent insufficient to induce acute effects;
- Development of a long-term strategic plan for research into the potential long-term health consequences of exposure to low-levels of chemical agents.

RESEARCH QUESTION 17

Can short-term, low-level exposures to pyridostigmine bromide, the insect repellent DEET, and the insecticide permethrin, alone or in combination, cause short-term and/or long-term neurological effects?

Statements that PB alone is safe and well tolerated are supported by a recent DoD-sponsored study (US Army, 1996) that investigated the side-effects of pyridostigmine bromide administered to healthy male and female volunteers in a double-blind protocol. PB (30 mg every 8 hours) or placebo was administered for 21 days (plus one dose). Anticipated side effects in the PB groups were observed although they ocurred in only a few subjects and were generally mild. Four out of 60 subjects receiving PB experienced diarrhea and abdominal pain. The gastrointestinal side effects are consistent with the muscarinic effects of PB. There were no differences in side effects between males and females. Vital signs, laboratory tests, and ECG were not different between PB and placebo groups. A one year follow-up showed no adverse long-term effects. A single subject was diagnosed shortly after the dosing phase with a Fixed Drug Eruption that resolved with topical steroid treatment. The IOM panel recommended that

the possibility of chronic neurotoxic effects from short-term low dose administrations needs to be tested in appropriate animal models (IOM, 1995; see Section 4.2, Health Outcomes).

Research Underway

PROJECT DoD-2: In addition to examining physiological and neurobehavioral effects of simulated pollutant exposures, laboratory animals will be tested with pollutants alone and in combination with PB.

PROJECTS DoD-21, 33: These projects investigate blood cholinesterase and the possible role variability in cholinesterase levels might play in predisposing some individuals to adverse reactions to otherwise low doses of anticholinesterases.

PROJECT DoD-37: This project is investigating the possible neurobehavioral and immunological responses of male and female rats to various combinations of PB, DEET, and permethrin.

PROJECT VA-5D: This project is investigating the interactive effects of pyridostigmine bromide and stress in a stress-sensitive animal model.

PROJECT VA-6C: This project is investigating in-vitro the combined neural effects of hydrocarbon solvents and pyridostigmine bromide.

PROJECTS VA-4A, 4B, 5A, 6A: Components of these projects are examining a variety of neurological and neuropsychological endpoints on selected cohorts of Persian Gulf veterans and Persian Gulf era veterans. Endpoints being examined range from nerve conduction velocity studies, to olfactory evoked potentials, to performance on computerized neurobehavioral test batteries. Results will be related to potential self-reported exposures to neurotoxic compounds.

Additional Research Needed

- The ongoing clinical and toxicological studies will determine the need for additional studies.

4.2.7 Psychological/Psychiatric Outcomes

A variety of symptoms have been reported by Persian Gulf veterans. Some symptoms may be related to post-traumatic stress disorder (PTSD). Published findings (Sutker et al, 1993; Sutker et al, 1994a,b; and Wolfe et al, 1993) suggest an increased prevalence of PTSD and other psychiatric diagnoses, such as depression, in some Persian Gulf veterans. Ursano and Norwood (1996) provide a comprehensive review of this issue. Although the prevalence of psychiatric disorders has been found to be lower in Persian Gulf veterans than among Vietnam veterans, it is evident that stressors during the Persian Gulf conflict were sufficient to cause significant psychiatric morbidity. Because of the low-level of combat experienced by many troops in the Persian Gulf conflict, the presence of psychiatric problems among some returnees suggests the

importance of stress other than actual combat as a precipitating factor. All three review panels (DSB, NIH, and IOM) recognized unusual stressors (e.g., sudden deployment, crowded living conditions, threat of CBW, combat) associated with the deployment and the possibility of their effects on mental health. Additionally, the potential effect of psychological stress on the immune system needs to be considered.

RESEARCH QUESTION 18

Do Persian Gulf veterans have a significantly higher prevalence of psychological symptoms and/or diagnoses than do members of an appropriate control group?

In a study of 1498 Seabees (Kaiser et al, 1995), service members who had been deployed to the Persian Gulf had higher scores on abnormal psychological variables.

Research Underway

PROJECTS VA-2, 4A, 5A, 6-Core, 7, 8, 12; DoD-1A, 1E, 6B, 30, 39, 40; HHS-1, 2: Components of these projects are collecting survey questionnaire data from which extensive questioning will allow development of prevalence estimates of psychological symptoms and diagnoses in comparison to an appropriate control. DoD 30 and DoD-39 will be focusing on women veterans and British veterans respectively. DoD-40 does not determine symptom or illness prevalence but is a longitudinal study of PTSD.

Investigators with the Boston VAMC Environmental Hazards Research Center have established collaborations with Japanese scientists to look at psychological/psychiatric outcomes in persons exposed to sarin in the Tokyo subway terrorist incident of June 1995. These investigators are also collaborating with Danish scientists who are studying Danish Persian Gulf veterans.

PROJECTS VA-4A, 5C, 6B: Components of these projects are examining the relationship between symptoms/symptom complexes (such as chronic fatigue syndrome) and the presence of any psychological symptoms and/or diagnoses.

PROJECT VA-4A, 5B, 5C: Components of these projects investigate the immunological status among different symptomatic groups of Persian Gulf veterans. Relationships between psychological stress and altered immune function are being explored.

Additional Research Needed

- The ongoing epidemiological and clinical studies will determine what, if any, additional studies are required.

4.2.8 Infection

Leishmaniasis

Unlike veterans with less well-defined illnesses, all but one of 12 veterans diagnosed with viscerotropic leishmaniasis had objective signs of disease, including high fever, lymphadenopathy and hepatosplenomegally. Nevertheless, because of the possibility of subclinical infection and the late presentation of this disease due to the prolonged incubation period, all three review bodies recommended further studies on detection and treatment of leishmaniasis. The IOM Committee recommended that when a serological test or other easy-to-use screening test(s) becomes available, an epidemiological and seroepidemiological study of leishmaniasis in Persian Gulf veterans should be conducted with appropriate controls. Although it appears now that infection with *L. tropica* is probably not a major risk factor for Persian Gulf veterans' illnesses, maintaining the current research effort is of value for potential concerns related to future deployments, and for taking advantage of research opportunities that could arise in the future.

Other Infections

Other infectious agents, such as mycoplasmas, bacteria, viruses, and fungi, are unlikely. Nevertheless, in spite of the absence of a strong case from clinical evaluations to support infectious agents as possible etiologic factors, targets of opportunity for collecting serological data should be exploited.

RESEARCH QUESTION 19

What is the prevalence of leishmaniasis and other infectious diseases in the Persian Gulf veteran population?

Research Underway

PROJECT VA-5A: As a component of this project, blood mononuclear cells from Persian Gulf veterans (from existing study populations) will be tested for reactivation for Epstein-Barr Virus, Cytomegalovirus, herpes-6, and herpes-7. Comparisons with appropriate control populations will be made.

PROJECT VA-15,16: These projects are directed at treatment and prevention of leishmaniasis.

PROJECT DoD-8A, 38: In DoD-8A a recombinant antigen has been characterized that detects immune response in patients with viscerotropic leishmaniasis. DoD-38 is also focusing on the development of skin and serologic assays for leishmaniasis.

PROJECT DoD-9: This project is attempting to identify the gene in humans that controls for tropism of *L. tropica* with the hope of determining which Persian Gulf

veterans, with latent *L. tropica* infection, are at risk for developing disease in the event of future immune suppression.

PROJECT DoD-12: This project involves the development of a forward-deployable infectious disease diagnostic laboratory.

PROJECT DoD-13: This project is examining dogs that were in the Persian Gulf theater to determine if they have any infections of importance to humans.

PROJECTS DoD-42, 47: These projects are investigating whether mycoplasma infection can be detected in individuals from a sample of Persian Gulf War veterans in comparison to a control group.

Additional Research Needed

- Because adequate serologic testing is not currently possible, the true prevalence of *L. Tropica* infection cannot be estimated. If such a test becomes available, seroepidemiologic studies may be undertaken. If feasible and practical, sera should be stored in expectation of such studies.

4.2.9 Cancer/Neoplastic Disease

The occurrence of some cancers among Persian Gulf veterans, although infrequent, has elevated concern over the possibility that these cancers may be linked to service in the Persian Gulf. The DSB, in examining the VA Persian Gulf Registry data, found no discernible demographic, military, or pathological pattern to the distribution of cancer cases (DSB, 1994). However, the DSB pointed out that any conclusions based on the Persian Gulf Registry must be made with caution because it is a self-selected group of veterans. The DSB also pointed out that because of the long latency period associated with cancer originating from environmental causes, it is too early to evaluate cancer risk in Persian Gulf veterans.

RESEARCH QUESTION 20

Do Persian Gulf veterans have a greater risk of developing cancers of any type when compared with an appropriate control population?

The mortality experience of Persian Gulf veterans compared with non-deployed era veterans has been investigated (Kang and Bullman, 1996). No disease-specific increase in mortality was observed in the deployed compared with the non-deployed veterans. Specifically, there was no difference in prevalence of death from neoplastic disease between Persian Gulf veterans and Persian Gulf era veterans. It has also been determined that there is no difference in hospitalization rates for neoplastic disease for Persian Gulf veterans compared with era veterans (Coate et al, 1995).

Research Underway

PROJECT VA-4C: A component of this project involves establishing the basis for a cancer surveillance system among Persian Gulf veterans in the state of Massachusetts.

PROJECT DoD-1F: This project is reviewing hospitalization records for both active duty and non-active duty veterans in California.

PROJECT DoD-7B: This project uses a rat animal model to investigate the carcinogenic potential of embedded depleted uranium fragments.

Additional Research Needed

- A system for examining cause-specific, long-term mortality among Persian Gulf veterans (see below) will be useful in providing information on future cancer mortality rates among Persian Gulf veterans.

4.2.10 Mortality Outcomes

RESEARCH QUESTION 21

Are Persian Gulf veterans experiencing a mortality rate that is greater than that of an appropriate control population? Are specific causes of death related to service in the Persian Gulf?

The cause-specific mortality experience of 695,292 service members deployed to the Persian Gulf during Operations Desert Shield/Desert Storm between August 1990 and April 1991 was compared to 746,038 non-deployed US service members (Kang and Bullman, 1996). Follow-up of these veterans covered the period beginning May 1, 1991, or the date they left the Persian Gulf area alive, and September 31, 1993. During the defined period there were a total of 1,765 deaths from all causes among deployed veterans while the number expected in a comparable US civilian population was 4,011. The observed deaths *due to all causes* among deployed Persian Gulf veterans was, however, greater than that in a comparable non-deployed military population during the same time period. These excess deaths among deployed veterans are primarily attributed to external causes, including all types of accidents and motor vehicle accidents. No excess deaths were observed for suicide and homicide among the Gulf veterans. Postservice increases in mortality due to external causes have been previously documented (Boyle et al, 1987). When deaths due to accidents, suicide, and homicide (external causes) were excluded (leaving only disease-related causes of death), the number of deaths among deployed veterans was 337 while the number expected was 382 based on the mortality rate among the non-deployed veterans. The computed disease-related death rates using these data are not different between deployed and non-deployed veterans. Despite the difference in overall mortality between deployed and non-deployed, DoD completed a study (Writer et al, 1995) comparing the one year, in-service mortality experience of service members who served in Operations Desert

Shield/Desert Storm to that of service members who served during the same time period but were not deployed to Southwest Asia. No difference in mortality over that period was found. The latter two investigations have only examined mortality rates over short time frames and, thus, cannot be used to draw any definite conclusions about Persian Gulf veterans' mortality over longer periods of observation time.

Research Underway

None

Additional Research Needed

- Mortality experience follow-up at appropriate future time-points.
- Investigation of the specific cause(s) of excess deaths by external causes in veterans deployed to war zones. Such an investigation should not be limited to the Persian Gulf War.

5. SUMMARY AND RECOMMENDATIONS

Since the end of the Persian Gulf conflict and the first reports of health problems in Persian Gulf veterans, the federal government has acted to ensure that veterans have access to medical care, can pursue appropriate avenues for compensation, and are informed of the various programs and activities made available to them by the VA and DoD. Research is now moving forward to address important questions, the answers to which will help guide health care professionals in their treatment of Persian Gulf veterans and will enhance our ability to minimize reoccurrence of such phenomena in future deployments. The *Working Plan* was developed in 1995 to bring coherence to the research efforts being conducted or sponsored by the federal government, and to assist federal decision makers in the pursuit of various research directions.

In the introduction, three goals were articulated for research on Persian Gulf veterans' illnesses:

1. Establish symptom and illness prevalence;

2. Identify risk factors; and

3. Identify diagnostic, treatment, and prevention methodologies.

The federal government is currently invested in all three goals and has made progress toward achievement of them. There are early indications that Persian Gulf veterans are reporting an excess of symptomatic complaints, but that these are somewhat diffuse in nature and not accompanied by any definite physical pathology. Results of mortality and hospitalization studies indicate that Persian Gulf veterans are not suffering from an excess of life-threatening diseases. It is evident, though, that the greatest need for research at the present continues to be in the area of epidemiology to ascertain symptom/illness/disease prevalence. Without definitive information in this regard it cannot be quantitatively determined whether Persian Gulf veterans are actually experiencing unusual or unexpected health problems; and if they are, the extent of the problem. The VA Persian Gulf Registry and the DoD Comprehensive Clinical Evaluation Program are valuable for revealing the nature of veterans symptoms and illnesses. However, they cannot, by their self-selected nature, reveal the true population prevalence of the reported symptoms and illnesses. Population-based studies are needed to obtain this information.

VA, DoD, and HHS are actively engaged in several population-based studies to determine symptom and illness prevalence. In addition, there are some small, highly focused, epidemiological efforts that are concentrating on ascertaining the prevalence of discernible symptom complexes such as chronic fatigue syndrome. Clinical investigations, as well as these ongoing epidemiological studies, are clearly important. In addition, concerns that arose more than a year ago about adverse reproductive outcomes and sexual dysfunction among veterans and their spouses added a new dimension to the problem. Although all of the major population-based studies have components associated with reproduction and sexual function, the 1995 *Working Plan* identified a need for studies focused on these particular problems. New projects (DoD-35 and to a certain extent DoD-30) will be addressing reproductive concerns.

As a vital adjunct to population-based studies, quantitative exposure information is needed. If there are findings of excess symptoms and illnesses in Persian Gulf veterans, geographical and temporal exposure data that can be assigned to veterans during their Persian Gulf deployment would greatly improve the prospects for determining an association between exposure and disease. Accurate exposure data has been difficult to obtain, and this will most likely continue to be a problem.

Research aimed at the second and third goals theoretically should wait until findings from population studies are complete. A few population-based studies have begun to yield results while others are scheduled for completion in the next 12 to 24 months. Although research studies aimed at these goals are not currently as important as the population studies, they have not waited for epidemiology findings. Appropriately targeted, parallel studies investigating specific etiologic factors anticipate epidemiology findings. Furthermore, the research questions that need to be posed addressing etiologic factors should have generalizablility beyond the current concerns of Persian Gulf veterans, and thus, address the needs of the third goal, i.e. the identification of diagnostic, treatment, and disease prevention methodologies. This is particularly important because some risk factors originally thought to be important have declined in likelihood as new information has become available.

The important contribution of non-federally funded research addressing common questions is recognized. Research by independent investigators, published in peer-reviewed scientific journals will continue to be evaluated and used in assessing the health consequences of service in the Persian Gulf, as well as adjusting the course of future research.

At the conclusion of the 1995 *Working Plan* several important specific areas of inquiry for which significant gaps in knowledge existed were listed. These areas of additional inquiry were cited in a Broad Agency Announcement (BAA) issued by DoD in 1995 in response to a Congressional mandate to conduct additional research by federal and non-federal investigators. The BAA sought proposals that were broadly directed toward epidemiology, clinical research, and research on pyridostigmine bromide. In June 1996 the Persian Gulf Veterans Coordinating Board announced the award of 12 new research grants as an outcome of the original BAA. These 12 were selected on the basis of scientific merit by an independent scientific review panel, and on programmatic relevance derived from the specific areas of inquiry identified in the *1995 Working Plan*.

As a result of the evolution of our understanding of Persian Gulf veterans' illnesses, and of events and concerns not known at the time of the *1995 Working Plan* (particularly the events at Khamisiyah and the bombings of Muhammadiyat and Al Muthanna), the Research Working Group has identified the following research issues that need further exploration in the near future:

- Follow-up of the mortality experience of Persian Gulf veterans, encompassing cause-specific mortality, at appropriate future time-points;
- More longitudinal follow-up studies of the health of Persian Gulf veterans, including those with illnesses that are difficult to diagnose;
- Critical peer-review of models used to predict exposure concentrations of environmental pollution (such as the Kuwait oil well fires) and chemical warfare

agents (such as the demolition of weapons storage sites at Khamisiyah in March, 1991 and aerial bombing of chemical weapons facilities during the air war);
- Assessment of the potential for clinical investigations of the health status of the service members in the vicinity of Khamisiyah when weapons bunker 73 and the storage pit were detonated in March, 1991. If deemed possible, such clinical investigations should be carried out.

Additional research on health-related issues arising from the Persian Gulf experience but with potential for more general applicability to future conflicts is also recommended, including:

- Investigation of the risk factors for the development of stress-related disorders, including, but not limited to, post-traumatic stress disorder (PTSD);
- Investigation of the risk factors responsible for the observed excess mortality due to external causes (e.g., motor vehicle accidents) in veterans of all wars and conflicts;
- Exploration of the development of practical, sensitive, and specific biomarkers of exposure to chemical agents, including organophosphate nerve agents and vesicants such as sulfur mustard.
- Toxicological and, where feasible, epidemiological research on the potential for long-term health effects resulting from low-level, sub-clinical exposures to chemical agents, particularly organophosphate agents such as sarin;
- Development of a strategic plan for research into the potential long-term health consequences of exposure to low-levels of chemical warfare agents;
- If a simple, sensitive and specific, as well as economical, test for *L. tropica* infection becomes available, seroepidemiologic studies may be undertaken in Persian Gulf veterans. Indeed, when feasible and practical, sera of veterans should be stored in expectation of the possibility for such studies. Despite the declining importance of *L. tropica* as a risk factor in Persian Gulf veterans, continued research on tests for *L. tropica* infection are valuable for potential future deployments.

It is anticipated that results from ongoing studies will become increasingly available during the coming year. Because of the limited and focused nature of these studies, it is essential that a contextual framework for evaluating these results be provided in order to maximize the value of results. Therefore, it is further recommended that researchers engaged in research on Persian Gulf veterans' illnesses be brought together in the coming year for the purpose of comparing results and developing strategies for further meaningful comparisons of results.

Just as this revision of the *Working Plan* was made necessary by advances in our understanding and new factual information in the past year, it is anticipated that the *Working Plan* will require periodic revision and updates in the future.

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APPENDIX

PERSIAN GULF VETERANS' ILLNESSES RESEARCH DATABASE FOR THE DEPARTMENT OF DEFENSE, DEPARTMENT OF HEALTH AND HUMAN SERVICES, & DEPARTMENT OF VETERANS AFFAIRS

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Title Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 1: A Study of Symptoms Among 1500 Seabees

Research Focus: Symptoms/General Health

Research Type: Clinical Epidemiology Research

Agency DoD

Study Location Naval Health Research Center

Study Start Date 6/1/94

Estimated Completion Date 10/1/96

Project Status Ongoing

DoD-1A

Summary

OVERALL PROJECT OBJECTIVE: To identify risk factors associated with reported symptoms in an effort to determine causes for possible Gulf War-related morbidity.
SPECIFIC AIMS: Are there differences in postwar morbidity between Gulf War veterans (GWV) and nondeployed veterans (NDV)?
METHODOLOGY: Seabees who were on Active-duty and had been so since September 1990 were eligible to participate. Seabees (Navy construction workers) were interviewed at two major Seabee bases, in Port Hueneme, CA; and Gulfport, MS. After signing a consent form, volunteers completed a questionnaire, provided blood and urine specimens, and had their height, weight, and hand-grip strength measured. A systematically selected subsample also performed a spirometry test. Whole blood, sera, and urine specimens were stored at -70°C. Sera were studied for evidence of infection while whole blood specimens may be characterized for genetic markers that may explain symptoms. Also, sera collected during this study will be compared to prewar sera, which are known to be available for a majority of the study population. Urine specimens may be used to rule out chronic diseases, such as adrenal insufficiency. Hand grip strength and spirometry results were compared among symptomatic and nonsymptomatic Seabees. The questionnaire responses will be used to compare the morbidity of GWV and NDV. Internal comparisons will be made among GWV using logistic regression modeling to determine if any specific exposures are associated with any symptoms or symptom complexes.
EXPECTED PRODUCTS (MILESTONES): A comparison of morbidity between GWV and NDV Seabees will be done. Survey screening tools will be developed for posttraumatic stress disorder, chronic fatigue syndrome, and three diagnostic symptom patterns. Assays will be performed on pre- and postwar sera as infectious or other agents are identified as plausible causes of morbidity among GWV. We have gained approval to do some limited testing of blood specimens, although the exact agents and schedule of testing has yet to be determined. Additionally, we are working on two spin-off studies looking at handgrip strength and lung function. Manuscripts are being prepared for publication.
STATUS/RESULTS TO DATE: Seabees (n=1498) were surveyed and studied. Deployed Seabees self-reported a higher prevalence of exposures and symptoms, as well as higher scores for abnormal psychological variables. Data analysis is nearing completion. Screening tools for disease outcomes have been developed and associations to various exposures have been measured. We have conducted more in-depth analyses into the symptom and exposure data using cluster analysis. We have developed additional studies focusing on handgrip strength and lung function and have prepared the results for presentation. We have also started drafting manuscripts for publication.

PUBLICATIONS

Kaiser KS, Hawskworth AW, Gray GC, et al. A comparison of self-reported symptoms among active duty seabees: gulf war veterans versus era controls. 123rd Annual Meeting and Exhibition of the American Public Health Association, Session 2198, 1995.

Title Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 2: A comparative study of hospitalizations among Active-duty personnel who participated in the Gulf War and similiar personnel who did not.

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency DoD

Study Location Naval Health Research Center

Study Start Date 7/1/94

Estimated Completion Date 10/1/96

Project Status Complete

DoD-1B

Summary

OVERALL PROJECT OBJECTIVE: Screen Department of Defense (DoD) hospitalizations for association with Gulf War deployment; identify specific diseases or disease groups that merit further study.
SPECIFIC AIMS: Are hospitalization rates from 1991-1993 the same for Gulf War veterans (GWV) and nondeployed veterans (NDV)?
METHODOLOGY: This is a tri-service, retrospective cohort study using hospital discharge records from all DoD facilities. The study population consists of 2 groups: nearly all active-duty personnel who deployed to the Persian Gulf any time between 1 August 1990 and 31 July 1991 (N = 578,492), and a comparison group consisting of a 50% random sample of personnel who were on Active-duty as of 30 September 1990 and did not deploy to the Persian Gulf before 31 July 1991 (N = 699,792). Hospitalization records for the subjects were supplied by the DoD Manpower Data Center from all military hospitals. Each hospitalization lists up to a maximum of 8 unique discharge diagnoses. Each discharge diagnosis was classified into 1 of the 14 major classifications of disease and injuries as defined by ICD-9-CM. Multivariate logistic regression was used to compute odds ratios for hospitalization of GWV relative to EV for all 14 categories. A Cox proportional hazards model is being used to compare risks of hospitalizations among a subset of these categories.
EXPECTED PRODUCTS (MILESTONES): Hospitalization risks for gulf war veterans. Results from this study were presented at the October 31, 1995 meeting of the American Public Health Association in San Diego, CA. The manuscript for this study has been submitted to the New England Journal of Medicine, and they have requested revisions to the manuscript.
STATUS/RESULTS TO DATE: A manuscripts is being prepared. In general, the deployed group was not at an increased risk of hospitalizations after the war as compared to non-deployed personnel. However, deployed personnel were at greater risk of hospitalization for mental illnesses. Supplementary analysis of specific diagnostic categories will follow. Completed data collection. Manuscript has been submitted for publication in the New England Journal of Medicine.

PUBLICATIONS

Coate BD, Anderson CM, Gray GC, Hyams KC, et al. Comparative study of hospitalization among gulf war veterans and era controls. 123rd Annual Meeting and Exhibition of the American Public Health Association, Session 2198, 1995.

Title Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 3: A comparative study of pregnancy outcomes among gulf war veterans and other active-duty personnel.

Research Focus: Reproductive Health **Research Type:** Epidemiology Research

Agency DoD **Study Location** Naval Health Research Center

Study Start Date 9/1/94 **Estimated Completion Date** 6/1/96

Project Status Complete DoD-1C

Summary

OVERALL PROJECT OBJECTIVE: To evaluate the risk of birth defects and other adverse pregnancy outcomes diagnosed in military medical treatment facilities (MTFs). Risk and relative risk of inpatient events will be assessed based on existing data.
SPECIFIC AIMS: Within the design parameters, are Persian Gulf War veterans (GWV) at higher risk of adverse pregnancy outcomes than nondeployed veterans (NDV)?
METHODOLOGY: This is a historical cohort study of reproductive outcomes among military personnel deployed to the Gulf War compared to military personnel who were not deployed. Demographic and hospitalization data are available for approximately 500,000 GWV and 700,000 NDV from the Department of Defense Manpower Data Center. Substantial demographic information is available on all subjects, including race/ethnicity, proxy measures of socio-economic status (rank and education), and military occupation. Data on inpatient services received at military are also available and diagnoses are recorded using ICD-9-CM codes. Risk and relative risks of major birth defects will be evaluated. Potentially confounding factors such as maternal age will be evaluated. Multivariate analysis will be conducted to estimate relative risks, controlling for identified confounders. Events among female service members will be considered separately from those among spouses of male service members.
EXPECTED PRODUCTS (MILESTONES): Risk and relative risks of major birth defects will be evaluated. Results from this study were presented at the October 31, 1995 meeting of the American Public Health Association in San Diego, CA. Manuscripts will follow.
STATUS/RESULTS TO DATE: Children born to the deployed group are being compared with children born to the non-deployed group (about 40,000 total births) for major birth defects noted during delivery. Completed data collection. Manuscripts currently being prepared.

PUBLICATIONS Cowan DN, DeFraites RF, Wishik SM, Gray GC, Kuhn J, et al. Preliminary analysis of birth defects and Persian Gulf air service. 123rd Annual Meeting and Exhibition of the American Public Health Association, Session 2198, 1995.

Title Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 4: Infertility and Miscarriage in Gulf War Veterans

Research Focus: Reproductive Health
Research Type: Epidemiology Research
Agency DoD
Study Location Naval Health Research Center
Study Start Date 11/1/94
Estimated Completion Date 9/1/97
Project Status Ongoing
DoD-1D

Summary

OVERALL PROJECT OBJECTIVE: To examine if there are differences between Gulf War Veterans (GWV) and nondeployed veterans (NDV) in rates of infertility and miscarriage.
SPECIFIC AIMS: Do GWV have higher rates of infertility, delayed conception, and early pregnancy loss compared to NDV?
METHODOLOGY: This study will be accomplished over two phases. The first phase will be a questionnaire given to 8,000 couples (where either the male, female or both partners were on active duty but did not participate in the Gulf War during the period of the war). The questionnaire will be sent to either male or female service members who were either married in 1991 or are currently married. The second phase will consist of a 20 minute telephone interview of approximately 5,000 couples and era comparisons to obtain further military exposure information, medical history, and other known risk factors for infertility and early pregnancy loss (eg. diet, smoking, and alcohol).
EXPECTED PRODUCTS (MILESTONES): Complete Phase I survey by December 1996.
STATUS/RESULTS TO DATE: Phase I instrument has been mailed to the selected individuals (n = 17,133) on 28 March 1996. Approximately 4,700 surveys have been received; another 1,800 have been returned undelivered, and 506 have been returned blank (non participating). Data entry, as well as acquisition of most recent addresses for undelivered surveys is under process. Phase I instrument has been remailed to 6,700 veterans on 5 July 1996.

PUBLICATIONS

Calderon RL, Wishik SM, Gray GC, Hiliopoulos K. The Persian Gulf war - effects on human reproduction. 123rd Annual Meeting and Exhibition of the American Public Health Association, Session 2198, 1995.

Title Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study.

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency DoD

Study Location Naval Health Research Center

Study Start Date 1/1/96

Estimated Completion Date 10/1/11

Project Status Ongoing

DoD-1E

Summary

OVERALL PROJECT OBJECTIVE: To study the health of Navy Seabees in relation to their deployments and the possible latent effects of Gulf War service.
SPECIFIC AIMS: 1. To determine if gulf war veterans have greater frequency of symptoms, illness, and propensity for making cognitive errors than other veterans. 2. To assemble a cohort for research on long-term effects of the gulf war on morbidity.
METHODOLOGY: The proposed study will be a nonconcurrent historical prospective study of all seabees who were on active duty for a least one month between August 2, 1990 and June 30, 1991. This group of approximately 17,500 current active duty, reservists, and former military personnel has been identified from records of the Defense Manpower Data Center. The study subjects will be mailed a survey to assess their current health status and their role (if any) in the Persian Gulf war. Participants in the survey will be followed prospectively for 15 years with a follow-up survey every 5 years (in 2001, 2006, and 2011) to detect possible latent effects of Gulf war on health. Potential sequelae include heart disease, diabetes, hypertension, arthritis, chronic inflammatory disease, psychiatric disease, and neurologic disease. To evaluate reliability of information, 2% of the survey participants will be interviewed by telephone and information on health and symptomatology from routine physicals wil be collected from military medical records. Bivariate and multivariate analyses will be used to identify risk factors associated with the outcomes of interest and multivariate logistic regression modeling will be applied to evaluate relationships between risk factors and the health outcomes. Development of latent chronic disease will be monitored by calculating the cumulative prevalance rates after each 5 year survey follow-up and comparing the baseline prevalence.
EXPECTED PRODUCTS (MILESTONES): Baseline and first telephone survey data showing initial symptom prevalences will be available by March 1996. Subsequent analyses of symptom and morbidity data from written and telephone surveys are expected by March 2001, March 2006, and March 2012. A comprehensive report showing comparisons between Gulf war veterans and other veterans including a summary of risk factor associations with morbidity will be completed by October 2011.
STATUS/RESULTS TO DATE: Pilot test of the survey instrument has been completed. Awaiting OMB approval. After OMB approval, the survey instrument will be finalized and mailed to approximately 17,000 Seabees/former Seabees. First results should be available in December 1996.

PUBLICATIONS none to date

Title Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 6: A Comparison of Nonfederal Hospitalizaton Experience Among Veterans in California who have separated from active service: PGW vs. EV.

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency DoD

Study Location Naval Health Research Center

Study Start Date 6/1/95

Estimated Completion Date 6/1/97

Project Status Ongoing

DoD-1F

Summary

OVERALL PROJECT OBJECTIVE: To determine if the federal and non-federal hospitalizations rates differed among Gulf War Veterans (GWV) and nondeployed veterans (NDV).
SPECIFIC AIMS: The specific research questions this project will address include:
Did the causes for hospitalization rates of GWV and NDV differ in (1) military and (2) nonfederal facilities?
Did the proportional distribution of causes for hospitalization differ during the prewar and postwar periods?
Did morbidity patterns differ between GWV and NDV, temporally, and by type of hospital?
METHODOLOGY: The study population will consist of GWV and NDV who resided in California after the Gulf War. Military hospitalization data will be obtained from The Department of Defense Manpower Data Center (DMDC). Each hospitalization lists up to 8 unique discharge diagnoses, which are classified into 1 of the 14 major classifications of disease and injuries as defined by the ICD-9-CM. Information on nonfederal hospitalization will be obtained for California residents from two sources: (1) The Office of Statewide Health Planning and Development (OSHPD), which maintains the Patient Discharge Data Program, a database of hospital discharge information from all nonfederally licensed hospitals in California and (2) the Department of Veterans Affairs Patient Treatment File (VAPTF) of all VA hospitalizations.
Two registry matches will be performed. The DMDC database will be matched with the OSHPD and the VAPTF files to obtain nonfederal hospitalization data for GWV and NDV.
The proportional distribution of causes for hospitalization of GWV and NDV during the prewar and postwar periods, and by hospital facility (military compared to nonfederal), will be computed through univariate and multivariate analyses.
EXPECTED PRODUCTS (MILESTONES): Hospitalization rates in military and nonfederal hospitals will be compared between separated and active duty GWV and NDV during the prewar and postwar periods.
Characteristics of morbidity resulting in hospitalizations at nonfederal hospitals for GWV and NDV will be described.
STATUS/RESULTS TO DATE: A computerized matching program was designed by the California OSHPD to enable linkage of their database of nonfederal hospital discharge information to a NHRC database consisting of identifying and demographic data for GWV and NDV. Negotiations for the terms of this collaboration are near completion. Data from NHRC will be provided to OSHPD, presumably Fall 1996.

PUBLICATIONS none to date

Title Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 7: Prevalence of Congenital Anomalies Among Children of Persian Gulf War Veterans.

Research Focus: Reproductive Health
Research Type: Epidemiology Research
Agency DoD
Study Location Naval Health Research Center
Study Start Date 6/1/95
Estimated Completion Date 6/1/97
Project Status Ongoing
DoD-1G

Summary

OVERALL PROJECT OBJECTIVE: To determine if the prevalance of congenital anomalies in the children born to Gulf War Veterans (GWV) exceed those of children of (1) nondeployed veterans (NDV) and (2) the general population (excluding GWV and NDV).
SPECIFIC AIMS: The specific research questions this project will address include: (1) Did the overall prevalence of congenital anomalies differ among infants of GWV, NDV, and the general population prior to and after the Persian Gulf War? (2) Did the diagnostic-specific prevalence of congenital anomalies differ among infants of GWV, NDV, and the general population prior to and following the Persian Gulf War? (3) What were the pathologic patterns of congenital anomalies among children born to GWV? How did these characteristics differ by military subpopulations (e.g., service, occupation, geographic location)?
METHODOLOGY: The Department of Defense Manpower Data Center (DMDC) maintains a database of demographic, military and hospitalization data among military personnel. The state health departments of Arizona, Arkansas, California, Georgia, Hawaii, Iowa, and Oklahoma conduct active surveillance of congenital anomalies through the initial 12 months of life. Live births and fetal deaths occurring after 20 weeks of gestation are recorded in the Birth and Death Certificate Records of the Vital Statistics Registries of these states.
Two registry matches will be performed. The DMDC database will be matched with the Vital Statistics Registry of each of these seven states to identify live births and fetal deaths occurring among conceptions of GWV and NDV between 1989 and 1993. Names common to the DMDC and Vital Statistics Registries will be matched with the Birth Defects Registry of each state. Overall and diagnostic-specific rates of congenital anomalies will be calculated and compared among infants of GWV and NDV and the general population (excluding GWV and NDV) of each state.
Chi-square and Fisher's exact (two-tailed) tests will be applied to compare rates between subpopulations. Stepwise logistic regression will be applied to identify characteristics associated with congenital malformations. Cluster analysis will be performed to detect interrelations among selected anomalies and subpopulations.
EXPECTED PRODUCTS (MILESTONES): The overall as well as diagnostic-specific prevalence rates of congenital anomalies, among children of GWV and NDV will be determined. Pathologic patterns of congenital malformations among children of GWV will be described, and may serve useful in developing hypotheses about genetically or environmentally-induced birth defects for future investigations.
STATUS/RESULTS TO DATE: Data provided by the Hawaii Birth Defects Monitoring Program are being analyzed to compare overall or organ-specific rates of birth defects among infants of GWV, NDV, and the civilian population. Data collection from the Arizona Health Department began in April 1996.

PUBLICATIONS none to date

Title Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET (short title: Toxicity of Simulated PGW Exposure)

Research Focus: Pyridostigmine Bromide **Research Type:** Basic Research

Agency DoD **Study Location** Ft. Detrick

Study Start Date 7/1/94 **Estimated Completion Date** 10/1/97

Project Status Ongoing DoD-2

Summary

OVERALL PROJECT OBJECTIVE: This project will evaluate the potential of a simulated Persian Gulf War (PGW) exposure consisting of multiple chemical exposures, alone and in conjunction with an imposed psychological stressor, to induce biological effects in Sprague-Dawley rats. Effects will be evaluated for similarity to symptoms and effects reported by exposed PGW veterans (e.g., "Persian Gulf Veterans' Illnesses"). No animal model for PGVI currently exists; therefore, the project will investigate if the rodent model can reproduce the symptoms reported in PGVI.
SPECIFIC AIMS: The primary research hyposthesis to be tested is that simultaneous exposure to a combination of chemical stressors, each well tolerated individually, causes subtle physiological changes when coupled with psychological stress. The study intends to identify, in Sprague-Dawley rats as an appropriate animal model, effects reported by humans similarly exposed during the PGW. The study also intends to identify a biomarker for use in evaluating the extent of exposure and of effect in humans. The study will investigate physiological and neurobehavioral effects, neurotransmitter levels, and changes in protein composition in serum/plasma, liver, kidney, testes, and brain from exposed rats.
METHODOLOGY: The chemical stressors and routes of exposure to be evaluated are: inhalation of fuel vapor (diesel, jet fuel) and their combustion products, dermal absorption of the insect repellent, N, N-diethyl-m-toluamide (DEET), and oral (or i.p.) administration of the anti-nerve agent enhancer, pyridostigmine bromide (PB). The psychological stress will be simulated by the intermittent administration of a mild electrical shock. The shock will be administered randomly by a computer controlled apparatus, so that to the experimental animal the shock will be uncontrollable and unpredictable; therefore functioning as a traumatic stressor. Male Sprague-Dawley rats will be exposed by inhalation to diesel and/or jet fuel vapor, orally to PB, and dermally to DEET, alone, and in various combinations. Half of the animals will receive a periodic, random, mild electrical shock as a psychological and neurobehavioral changes by standard tests, immediately after exposure and after a 60-day latent period. At sacrifice, neurotransmitter levels; protein mapping (i.e., stress protein induction) in brain, testes, kidney, liver, and serum/plasma; neurotoxic esterase and acetylcholinesterase activity; clinical chemistry, and immune function will be measured.
EXPECTED PRODUCTS (MILESTONES): This study will evaluate the potential of a simulated Persian Gulf War (PGW) exposure consisting of multiple chemical exposures, alone and exacerbated by an imposed psychological stressor, to induce toxic effects in Sprague-Dawley rats similar to those reported by Persian Gulf veterans experiencing symptoms thought by some to be related to the Persian Gulf War. Currently, no animal model for PGVI exists. This study will investigate, in a rodent model, factors that may have contributed to the development of the symptomatologies reported in PGVI. Representative chemical exposures from the PGW theater, with and without an imposed psychological stressor, will be investigated individually and in combinations to determine possible interactive effects. Selected physiological and neurobehavioral tests, neurotransmitter levels, and expression of stress proteins and/or shifts in protein charge characteristics will be used to correlate findings observed in Sprague-Dawley rats with the physiological and psycholgical symptoms commonly reported in PGVI.
STATUS/RESULTS TO DATE: Ongoing. Animal exposure system modified to administer electric shock as psychological stressor was successfully tested. The fourteen day exposure of male Sprague-Dawley rats to inhaled JP4 jet fuel vapor, oral pyridostigmine bromide, and dermal DEET has been successfully completed. The first data set has been collected and is being analyzed. The second data set was collected in mid-September and data analysis will continue until December

1996.

PUBLICATIONS Nelson RA. Determining Types of Health Effects to Persian Gulf Veterans Due to Exposure to Occupational Hazards, Thesis No. AFIT/GEE/ENV/95D-13, Air University, USAF Institute of Technology, Wright-Patterson Air Force Base, OH. 1995.

Title The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 9/1/92

Estimated Completion Date 5/20/94

Project Status Complete

DoD-4

Summary

OVERALL PROJECT OBJECTIVE: Assess the general sense of well-being of Gulf War era veterans in the States of Hawaii and Pennsylvania.
SPECIFIC AIMS: Identify groups within the population reporting physical or mental distress and highlight probable causes or contributing factors. Ascertain whether any group within this population was at risk for future development of PTSD related to their Gulf War era experiences. Evaluate the status of the 14th Quartermaster Detachment. Assess the impact of the casualties of the 14th Quartermaster Detachment on the community of Greesburg, Pennsylvania.
METHODOLOGY: Identified citizens of Pennsylvania and Hawaii who served during the period of Operation Desert Shield/Storm (16, 167). Solicited voluntary participation in completing questionnaires, interviews, and other study materials (approx. 14,100). Designed and administered study materials (4,334 responses). Integrated data from an additional 25,000 individuals being studied as part of a larger assessement as a sample population from which to draw inferences. Survey instruments and methods included a questionnaire, Impact of Events Scale, Brief Symptom Inventory, PTSD Risk Algorithm, records/reports from Pacific Center for PTSD and from PTSD Clinical Team, VA Medical Center, Pittsburgh, PA. A variety of statistical analyses were applied to the data, scores, and indices. The distribution of psychological symptoms in the samples was analyzed, as was the distribution of illness symptoms as another category of risk. The significance of the differences in psychological and physical symptoms between deployers and nondeployers was examined.
EXPECTED PRODUCTS (MILESTONES): An assessment of the general physical and mental well-being of the subject population. Information to assist Congressional determination of the need for appropriated funds for specialized counseling and support services to counter any adverse effects of service during Operation Desert Shield/Storm. Information addressing potential links between service in the Gulf and subsequent health and adjustment difficulties upon return.
STATUS/RESULTS TO DATE: Study completed. Results published. The studied population was generally well-adjusted, with subgroups experiencing either physical symptoms, high levels of stress, or both (about 15% of the population). Among those deployed and who reported physical symptoms, neither stress nor exposure to combat or its aftermath bear much relationship to their distress; only the fact of deployment differentiates them from their less-burdened counterparts. About 15% of those deployed were experiencing both stress and physical symptoms at the time of the study. Many of these seem at risk for development of further difficulty, particularly PTSD.

PUBLICATIONS US Army Medical Research and Materiel Command Report. The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey. May 1994.

Title Combat Stress Pharmacotherapy

Research Focus: Brain & Nervous System

Research Type: Basic Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 10/1/88

Estimated Completion Date 9/30/99

Project Status Ongoing

DoD-6A

Summary

OVERALL PROJECT OBJECTIVE: Combat stress reaction (CSR) and posttraumatic stress disorder (PTSD) are thought to be part of a common spectrum of disorders. It is essential to develop animal models for combat stress reaction, to identify neurochemical mechanisms of, and pharmaceutical countermeasures for combat stress effects. Emphasis is on rapidly acting countermeasures which could be administered far forward, and which would allow the stress casualty to remain on duty and prevent the development of PTSD. Pharmaceutical countermeasures must be free of unwanted side effects, such as sedation or impairment of memory or performance.
SPECIFIC AIMS: Evaluate clinical and pre-clinical pharmaceuticals to prevent/reverse conditioned defeat (CD). Use acoustic startle, the swim test, neuroendocrine markers and telemetric monitoring of heart rate in behaving, unrestrained animals exposed to threat, develop technology for predicting vulnerability to conditioned defeat; thus enhancing evaluation of possible preventive measures.
EXPECTED PRODUCTS (MILESTONES): FY 97: Examine the effect of valium on CD in another species (mice) to test the generality of the finding that valium may exacerbate CD (and might be contraindicate in combat stress reaction). Extend testing to include benzodiazepine antagonists and inverse agonists in mice. In addition, begin testing Buspirone, a clinically available, non-sedating, non-benzodiazepine anxiolytic drug in mouse CD model. Will also test its more potent pre-clinical analogs - Gepirone, ipsapirone, and tiaspirone. The startle response has been reported to be exaggerated in both CSR and PTSD. Accordingly, we will test the effect of CD on acoustic startle in the mouse. To identify potential aids to diagnosis of risk for CSR, we will further characterize hormonal responses to CD. FY 98: Begin testing other behaviorally active clinically-available drugs in mouse CD model: (a) beta blockers (atenolol); (b) antidepressants used in panic disorders (Prozac, tricyclics); (c) stimulants such as caffeine and amphetamine. Evaluate all listed compounds for capability to reverse CD-induced deficits in the swim test. FY 99: Begin testing novel pre-clinical, non-benzodiazepine anxiolytics in the mouse CD model, including cholecystokinin antagonists; corticotrophin releasing hormone antagonists; and Neuropeptide Y (NPY) agonists. Evaluate potential therapeutic effects of thyretropin releasing hormone (TRH) - an endogenous peptide stimulant successfully employed to reverse learned helplessness. Target drug intervention at specific brain sites, study viable brain slices from defeated mice, including amygdala and hippocampus, to evaluate agents for selective effects on specific circuits involved in CD. Study the effects of CD on cognitive function and neurodegeneration.
STATUS/RESULTS TO DATE: By establishing a streamline model of conditioned defeat (CD), we have met the requirement of developing an animal model for testing diagnostics for component processes of combat stress reaction (CSR) and screening drugs for safe, rapid treatment. We have shown that CD markedly decreases activity in the swim test - a measure used in the pharmaceutical industry to screen antidepressants. In an effort to develop reliable predictors and clinical indicators for CSR, we have characterized the dramatic responses to CD of hormones stimulated via the anxiogenic peptide, corticotrophin releasing hormone (CRH). We have shown that acoustic startle response (ASR) in hamsters was exacerbated by administration of CRH. This is significant because exaggerated acoustic startle response has been validated as a bilogical marker for PTSD and reported as a symptom of CSR as well. We found that valium is clearly counterproductive as a treatment for hamsters, as it markedly exacerbated CD. Thus, the CD

model affords us the capability of identifying drugs which might be contraindicated, as well as those which might be beneficial. By way of confirmation, an Israeli colleague is reporting that benzodiazepines fail to block the development of PTSD following trauma. We have optimized the CD model as a test bed for screening drugs by modifying it to deliver rapid, high-volume, low-cost throughout.

PUBLICATIONS

Hebert M, Potegal M, Moore T, Evenson AR, Meyerhoff J. Diazepam exacerbates conditioned defeat in hamsters (Mesocricetus auratus). Pharmacology, Biochemistry and Behavior. In press. 1996.

Potegal M, Ferris C, Hebert M, Skaredoff L, Meyerhoff J. Attack priming in female Syriahn golden hamsters is mediated by a c-fos coupled process within the corticomedial amygdala. Neuroscience. In press. 1996.

Potegal M, Hebert M, deCoster M, Meyerhoff J. Brief, high frequency stimulation of the corticomedial amygdala induces a delayed and prolonged increase of aggressiveness in male Syrian golden hamsters. Behavioral Neuroscience 110(2):1-12, 1996.

Title Combat Stress Diagnosis, PTSD Prevention

Research Focus: Brain & Nervous System

Research Type: Clinical Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 10/1/87

Estimated Completion Date 9/30/98

Project Status Ongoing

DoD-6B

Summary

OVERALL PROJECT OBJECTIVE: Develop diagnostic instruments for far-forward, early diagnosis of soldiers at risk for combat stress reaction (CSR) and posttraumatic stress disorder (PTSD) to allow early intervention to prevent chronic PTSD.
SPECIFIC AIMS: Use combined neuroendocrine and psychophysiologic techniques to develop rapid, reliable and inexpensive means of determining soldiers' level of stress, fitness for duty and risk of CSR/PTSD.
METHODOLOGY: We will measure salivary levels of cortisol, testosterone, and dehydroxyepiandosterenedione sulfate (DHEAS) as stress indices. We will critically evaluate the reliability of voice frequency modulation as a stress index. In collaboration with the New Haven Veterans Administration we will conduct a prospective study on risk of stress reactions/PTSD in Special Operations Forces.
EXPECTED PRODUCTS (MILESTONES): FY 96: Correlate salivary cortisol and Soldier of the Month Board performance; measure effect of stress on salivary testosterone and DHEAS. FY 97: Determine effect of psychological stress on voice frequency modulation spectrum and correlate with performance as well as physiological and hormonal changes. FY 98: Complete prospective study of changes in acoustic startle and dexamethasone suppression tests (using salivary cortisol measurements) in soldiers subjected to stressful deployments.
STATUS/RESULTS TO DATE: Ongoing. Because the "Soldier of the Month (SOM) Board" is a uniquely robust physiological stressor, we have been using it as a test bed to develop and validate field-ready stress measures, such as a battery of non-invasive (salivary) hormonal measures. We will use these measures in stress studies in soldiers at risk for combat stress reaction and/or PTSD during military operations in the field. We have characterized the psychoendocrine and autonomic profile of operational stress, using the SOM Board as a model. Elevated plasma and salivary cortisol levels were measured in soldiers after an SOM Board experience. We have identified several plasma hormones which correlate positively with anxiety, and have demonstrated that anticipatory anxiety predicts poor performance.

PUBLICATIONS

Pitman RK, Orr SP, van der Kolk BA, et al. Analgesia: a new dependent variable for the biological study of PTSD, In Post Traumatic Stress Disorder: Etiology Phenomenology and Treatment (ed by Wolf ME). American Psychiatric Press, pp 141-147, 1990.

Title Health Risk Assessment of Embedded Depleted Uranium: Behavior, Physiology, Histology, and Biokinetic Modeling

Research Focus: Depleted Uranium
Research Type: Basic Research
Agency DoD
Study Location Ft. Detrick
Study Start Date 12/1/94
Estimated Completion Date 1/30/98
Project Status Ongoing
DoD-7A

Summary

OVERALL PROJECT OBJECTIVE: To evaluate health risks associated with tissue-embedded depleted uranium (DU) fragments by studying the behavioral, physiological, and histological consequences of implanted DU in a rodent model.
SPECIFIC AIMS: Specific evaluations in the DU implanted rodent model will include: 1. Behavioral tests of motor activity and memory. 2. Nerve conduction studies of peripheral nerve function. 3. Measurement of central nervous system excitability in brain slice preparations. 4. Biochemical assessments of renal function. 5. Histological assessment of local tissue damage and capsule formation. 6. Measurement of tissue concentrations of uranium. 7. Development of a biokinetic model describing the distribution of uranium over time.
METHODOLOGY: After defining appropriate doses to be used for analysis of DU effects, a study of 325 rats provides toxicity data. Rats are randomly assigned to 5 treatment groups: 1) low-dose DU, 2) medium-dose DU, 3) high-dose DU, 4) tantalum (Ta) controls, and 5) non-implanted sham-surgical controls. In the low-dose and medium-dose groups, Ta is substituted for a fraction of the DU pellets to keep the total number of implanted fragments constant. Rats are evaluated, euthanized and tissue samples taken at 1, 6, 12, or 18-months following fragment implantation. Groups of 15 rats were determined to be necessary to achieve statistical significance. Additional animals (20 rather than 15) are implanted for the 18-month time point with the expectation of a 20-25% natural mortality. Each rat is thoroughly evaluated for changes in behavior (functional battery, motor activity, passive avoidance test), peripheral nerve function (conduction velocity measurements), CNS excitability (hipocampal brain slice electrophysiology), renal function (plasma and urine biochemistries) and tissue histology including capsule formation. In addition, data on tissue uranium levels (measured by kinetic phosphorescence analysis) from a subgroup of rats is used to develop a biokinetic model to predict uranium distribution. All measured parameters are compared among groups through anlysis of variance and significance accepted at the $P<0.05$ level.
EXPECTED PRODUCTS (MILESTONES): Determine appropriate doses for a DU toxicity study in the rat: July 1995. Complete toxicity assessment at the one-month point: Dec 1995. Complete toxicity assissment at the six-month point: Dec 1996. Complete toxicity assissment at the 12-month point: June 1997. Complete toxicity assissment at the 18-month point: Dec 1997. Complete biokinetic modeling for distribution of DU fragments: Jan 1998.
STATUS/RESULTS TO DATE: Ongoing. The 30-day data following pellet implantation is complete. Fibrous tissue adheres to DU but not Ta pellets in situ, but capsule formation is not yet evident. Uranium levels are high and dose-dependent in kidney, bone, and urine and moderately high in muscle, brain and spleen. There is no evidence of renal toxicity or neurobehavioral neurotoxicity at this time and point. Results have not yet been published.

PUBLICATIONS none to date

Title Carcinogenicity of Depleted Uranium Fragments

Research Focus: Depleted Uranium **Research Type:** Basic Research

Agency DoD **Study Location** Ft. Detrick

Study Start Date 1/26/95 **Estimated Completion Date** 10/30/98

Project Status Ongoing DoD-7B

Summary

OVERALL PROJECT OBJECTIVE: To assess the carcinogenic risks associated with long-term exposure to DU-containing shrapnel in wounds.
SPECIFIC AIMS: 1. Determine the carcinogenicity of radioactive DU fragments in tissues relative to nonradioactive (tantalum) foreign-body fragments. 2. Correlate urine and kidney concentrations of Uranium with time after implantation of DU fragments.
METHODOLOGY: 1. Relative Carcinogenicity of Embedded DU Fragments. Test metals, in the form of wires or thin foils, will be surgically implanted into the subcutis of rats. Thorotrast will be used as a positive control radioactive material. These animals will be observed for two years for the onset, incidence, and biological characteristics of tumors developing at the site of implantation. The study will determine if radioactivity of DU foils will increase the carcinogenicity of larger foils, or make smaller foils carcinogenicity of tantalum foils of similar sizes. The incidence of subcutaneous tumors will be compared among dose groups by using a Cox proportional hazards model. 2. Renal Toxicity of Chronic Uranium Exposure. This study will determine the time course to achieve a steady-state renal DU concentration from an implanted source and to determine if toxicity is present at the steady-state concentration. A pilot study in rats will be conducted to determine if the urinary excretion of U from implanted DU foils is sufficiently high enough above background to detect. Urinalysis will be performed on 24-hour urine samples after animals have been acclimated to the metablolism cages. Analyses will include U concentration, pH, glucose, protein, and creatinine. Urinary enzymes will be measured for possible use in the renal toxicity study. If elevated U concentrations can be detected in the urine, the renal study will be conducted as a subset of the carcinogenesis study. Rats that are sacrificed will be examined for lesions, with particular attention to the urinary system. Kidneys will be examined histologically for lesions related to U toxicity. U content in the kidney and skeleton and remainder of the carcass will be determined. Laser phosphorim will be used to analyze tissue and urine samples for U.
EXPECTED PRODUCTS (MILESTONES): The carcinogenic hazard of radioactive DU fragments relative to nonradioactive fragments will be determined so that informed judgements can be made about the clinical management of veterans with DU fragments embedded in their soft tissues. Milestones of this study are: January 1996: Completion of pilot study. April 1996: Initiation of the long-term study of potential carcinogenic effects of implanted DU fragments. April 1998: Completion of the long-term carcinogenesis of DU fragments. October 1998: Final Report.
STATUS/RESULTS TO DATE: Ongoing. Dr. Gerhard Brand visited the Inhalation Toxicology Research Institute March 1995 to consult on the experimental design of studies using subcutaneous implants of metal in rodents. Dr. Brand developed the animal model system which is the basis for the planned carcinogenesis studies. Dr. Hahn visited the Armed Forces Radiobiology Research Institute to discuss and coordinate research approaches to the problems of DU toxicity with Armed Forces Radiation Research Institute (AFRRI) investigators. 1. A preliminary 60-day study protocol has been initiated to a) determine the early solubility of implanted DU compared with DUTi in rats and mice; b) determine the early histologic responses to implanted DU or DUTi and determine the changes in surface characteristics of DU or DUTi that may alter the long-term potential carcinogenic effects of implanted DU. This study will determine the feasibility of using a subcutaneous implantation model of foreign body carcinogenesis. 2. A significant change from initial proposal is the addition of DU (0.75% Ti) alloy as a companion with DU. Discussions with investigators at AFRRI indicated that differences in solubility may exist between these two compounds. 3. Mice were included in the pilot study since the foreign body carcinogenic model

being studied has used both rats and mice. Certain strains of mice develop foreign body sarcomas much more rapidly than other strains of mice or rats.

PUBLICATIONS none to date

Title Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL)

Research Focus: Leishmaniasis **Research Type:** Applied Research

Agency DoD **Study Location** Ft. Detrick

Study Start Date 10/1/93 **Estimated Completion Date** 9/1/96

Project Status Complete DoD-8A

Summary

OVERALL PROJECT OBJECTIVE: To develop a reliable serologic test for viscerotropic leishmaniasis.
SPECIFIC AIMS: Goal is to identify an antibody (Ab)-based serologic assay to detect active infection with Leishmania parasites causing the clinical syndrome of VTL using a standard format such as enzyme-linked immunosorbent assay (ELISA).
METHODOLOGY: Use of ELISA-based assays to diagnose active infection with an infectious agent is a widely accepted and useful diagnostic intervention. Currently, there are no commercially available serologic assays to detect Leishmania infection. Some specialty labs use the indirect immunoflurescence technique (IFAT) format to detect antibodies to surface proteins of the promastigote (insect vector form of the parasite); however, the IFAT is not useful in VTL. Once the parasite is injected into humans by the sand-fly vector, it transforms into an amastigote (the form found in mammals). The amastigote is a genetically different morphologic form which expresses a unique repertoire of antigens. We believe these amastigote dominant antigens hold the key to serologic diagnosis of VTL. Using recombinant molecular biology techniques, proteins which are recognized by VTL sera can be made in large quantities and used as capture antigens in ELISA tests.
EXPECTED PRODUCTS (MILESTONES): Identification of reactive clones made from screening a genomic library of Leishmania DNA, cloning and sequencing the recombinant proteins and use of the recombinant proteins to screen sera from patients with VTL.
STATUS/RESULTS TO DATE: A genomic library was made from a Desert Storm isolate of Leishmania. Parasite DNA was sheared and introduced into E. coli via phage virus. Bacterial clones with eparasite DNA were transferred to nitrocellulose and then incubated with radioidinated protein labeled VTL sera. Reactive clones were then isolated, induced, and protein was sequenced. Patients with VTL appear to recognize a 210 kd recombinant protein, called Lt-1, the carboxy third of the protein is made of repeats. Smaller recombinant proteins and synthetic peptides based on the repeats have been made. To date, none of these peptides reliably discriminates infected from noninfected samples. Further work in this area is being done by the contractor.

PUBLICATIONS

Dillon DC, Day CH, Whittle JA, Magill AJ, Reed SG. The molecular and immunological characterization of Leishmania tropica antigens: serological and cellular responses by viscerotropic Leishmaniasis Patients. VIII Intern Congress of Parasitology, 1994.

Dillon DC, Day CH, Whittle JA, Magill AJ. Reed. The Molecular and immunological characterization of Leishmania tropica antigens: serological and cellular responses by Viscerotropic Leishmaniasis Patients. 43rd Annual Mtg AM SocTrop Med & Hyg., 1994.

Dillon DC, Day CH, Whittle JA, Magill AJ, Reed. Characterization of a Leishmania tropica antigen that detects immune responses in Desert Storm Viscerotropic Leishmaniasis patients. Proc. Natl Acad Sci., (92) :7981-82, August 15 1995.

Title Development of a Leishmania Skin Test Antigen (LSTA)

Research Focus: Leishmaniasis
Research Type: Applied Research
Agency DoD
Study Location Ft. Detrick
Study Start Date 10/1/93
Estimated Completion Date 1/31/00
Project Status Ongoing
DoD-8B

Summary

OVERALL PROJECT OBJECTIVE: To develop a reliable skin test for Leishmania infection.
SPECIFIC AIMS: Goal is to identify a safe, potent and non-sensitizing LSTA; manufacture it under cGMP; and obtain an IND for its use in phase 1 and phase 2 clinical trials.
METHODOLOGY: Use of skin tests to diagnose prior infection with an infectious agent (e.g., tuberculosis) is a widely accepted useful diagnostic intervention. Currently there is no Leishmania skin test licensed for use in the USA or available under an IND. Once required phase 1 and phase 2 studies are completed in humans, studies could be performed in Gulf War veterans with confirmed and suspected leishmaniasis.
EXPECTED PRODUCTS (MILESTONES): Completion of the IND application by 4th Quarter FY96 and completion of phase 1 study by 2nd Quarter FY97. Phase 2 trials in FY97-98. Phase 3 trials in 98.
STATUS/RESULTS TO DATE: Ongoing. A lot of LSTA (microfluidized-lysate (MFL) - LSTA) was manufactured under cGMP in May 1995. Pre-clinical testing in guinea pigs and non-human primates has shown it to be safe and potent. A similar product has sensitized naive guinea pigs on repetitive testing but whether this will occur in humans is not known. SDS-PAFE analysis of product substance, final container product and following heat treatment has shown the MFL-LSTA to be stable. IND submitted to FDA on 6/2/96. FDA placed phase 1 protocol on clinical hold on 7/2/96 pending satisfactory response to questions relating to product safety. We believe we will be able to satisfactorily address the FDA concerns.

PUBLICATIONS

Stitler JM, Ballou WR, Eckels KH, Magill AJ. Good Manufacturing Practices (GMP) Production of Leishmania Skin Test Antigen: 1. Protocol Requirements for Investigational New Drug (IND) Application. 43rd Annual Mtg of AM Soc Tropical Med & Hyg. 1994.

Stitler JM, Ballau WR, Eckels KH, Wellde BT, Topper MJ, Rowton ED, Magill AJ. Good Manufacturing Practices Production of Leishmania Skin test antigen: 2. Production of a Microfluidized Lysate. 44th Annual Mtg of AM Soc Tropical Med & Hygiene, 1995.

Title Identification of the Genetic Factors Which Control Tropism in Leishmania

Research Focus: Leishmaniasis **Research Type:** Basic Research

Agency DoD **Study Location** Ft. Detrick

Study Start Date 7/1/94 **Estimated Completion Date** 7/1/98

Project Status Ongoing DoD-9

Summary

OVERALL PROJECT OBJECTIVE: To identify the gene(s) that control tropism in Leishmania and determine its (their) sequence and function.
SPECIFIC AIMS: The goal of this DOD/VA research is to identify the gene(s) that control tropism in Leishmania. The identification of a "tropism" gene will: (a) Enable the development of specific gene probes (primers) to be used in a patient screening program to identify those at risk of reactivation of latent infections; (b) Address the fundamental question of infectious disease pathophysiology, namely why an organism infects a particular cell; (c) Optimize treatment regimens according to Leishmania species and the immune status of the host. The identification of the genetic factor(s) involved in the visceralizaiton of Leishmania will require us to develop in vitro and in vivo models of tropism to facilitate the study of viscerotropic leishmaniasis (diagnosis, therapy, prevention) and Leishmania tropism.
METHODOLOGY: A. Develop in vitro and in vivo models of Leishmania tropism to use for the determination of the genetic factors controlling tropism: i) a promastigote temperature sensitivity model; and ii) a cutaneous and a visceral animal model of Leishmania tropism. B. Create Leishmania mutants with altered tropism in the in vitro and in vivo models of tropism: i) temperature sensitive parasites changed to resistant and visa versa; and ii) cutaneous parasites (in the animal model) changed to visceral and visa versa. C. Use recently developed molecular genetic techniques to restore the original (wild-type) phenotype to the Leishmania temperature and tropism mutants by transfection with the appropriate Leishmania cosmid DNA libraries. D. Identify the gene(s) controlling temperature sensitivity and tropism present in the cosmid(s) which restore(s) a wild-type phenotype to the Leishmania cells. E. Retest the function of these genes in both models using transfection methodology.
EXPECTED PRODUCTS (MILESTONES): 1. Develop an in vitro temperature sensitivity model that will correlate with tropism in vivo - 1995. 2. Develop animal models which can be used to select for altered tropism - 1995. 3. Obtain Leishmania mutants in vitro - 1995 - 1996. 4. Obtain Leishmania mutants in vivo - 1996 - 1997. 5. Create cosmid DNA libraries - 1996 - 1997. 6. Reconstitute the wild-type phenotype (tropism) utilizing a wild-type Leishmania DNA cosmid library - 1997-1998. 7. Molecular characterization: a) Identify the gene(s) present in the cosmid(s) which restore(s) a wild-type phenotype to the Leishmania mutants. b) Sequence the gene(s) - 1998. c) Determine homologies with genes in the database - 1998.
STATUS/RESULTS TO DATE: Ongoing. 1. Developed an in vitro promastigote temperature model and determined that temperature sensitivity in vitro correlates with Leishmania tropism in vivo. 2. Determined that there is no absolute temperature requirement for dermotropism, but that there is a minimum temperature resistance requirement for visceralization. 3. Determined that parasite strains that have an unusual tropism in the human host (to include the viscerotropic L. tropica from Desert Storm) also show an unexpected temperature sensitivity in the model. 4. Developed two animal models where the tropism of the Leishmania strain is known, uniform, and reproducible (all organisms are found in one location, either visceral or cutaneous) when inoculated in the skin (sc) to mimic a sand fly bite: Cutaneous model - no visceralization; and Visceral model - no skin lesions. 5. Obtained Leishmania temperature sensitive and resistant mutants. 6. Developed and standardized in the laboratory transfection and Leishmania cosmid DNA library techniques. 7. Selected a L. donovani and two L. tropica temperature-resistant strains in vitro. 8. Chemically mutagenized a L. mexicana strain and selected a tropism mutant in our hamster model. 9. Made wild-type DNA cosmid librarios of all the Leishmania strains (4) that will be mutagenized and

selected for altered tropism in our hamster model.

PUBLICATIONS

Callahan HL, Portal IF, Grogl M. Development of an in vivo Leishmania temperature sensitivity model: preliminary studies with strains with aberrant tropism in vivo. 44th Annual Meeting of Am Soc Tropical Med & Hygiene 53(2):215, 1995.

Callahan HL, Portal IF, Bensinger SJ, Grogl M. The temperature sensitivity of Leishmania promastigotes in vitro: a model for tropism in vivo. 1996. Accepted, Exp. Parasit.

Callahan HL, Grogl M. Development of animal models to study Leishmania tropism at the molecular level. 1995, in preparation for submission to the Am J Tropical Med.

Title Pyridostigmine Synergistic Toxicity Study

Research Focus: Pyridostigmine Bromide **Research Type:** Basic Research

Agency DoD **Study Location** Ft. Detrick

Study Start Date 11/1/94 **Estimated Completion Date** 3/1/94

Project Status Complete DoD-10

Summary

OVERALL PROJECT OBJECTIVE: To determine potential toxic interactions when pyridostigmine bromide, permethrin, and DEET are given concurrently to male rats by gavage. The after-action analyses uncovered concerns about the possible synergism of pyridostigmine taken by the service members (SM's) in ODS to protect them against potential nerve agent exposure and permethrin and DEET, insecticides used by SM's in ODS.
SPECIFIC AIMS: Phase I determined the acute oral lethal dose response relationship of each compound with the vehicle, propylene glycol. Phase II was a dose response study using probit units from Phase I as well as calculated dosage solutions of the three materials in combinations.
METHODOLOGY: The first phase was the development of acute oral lethal dose-response relationship of each compound with the vehicle, determine dosage levels for the second phase. Part 1 of Phase II served as a positive control for the interaction portion of the study and verified data obtained from Phase I. The Part 1 dose response study used probit untis from Phase I. Part 2 of Phase II was similar to the control portion except that the vehicle contained the calculated LD16 of the other two compounds. All studies were conducted under Good Laboratory Practice (GLP; 40 CFR 160 and 792 and amendments). The Phase I study protocol used 16 groups of 10 animals each, with one group of 10 receiving only the prolylene glycol vehicle. Gross necropsy was performed on all animals as soon as possible after death. Animals surviving the 14 day study period were sacrificed and examined for gross pathological lesions. The Phase II study used 15 groups of six animals each for the positive control portion and 18 groups of 10 animals each for the interaction portion. Animals were necropsied and examined for gross pathological lesions.
EXPECTED PRODUCTS (MILESTONES): Reports and publications.
STATUS/RESULTS TO DATE: Complete. Report published 31 May 1995. The principal finding is that there is significant increase on the lethal effect in rats given pyridostigmine bromide, permethrin, and DEET simultaneously by gavage when compared to expected additive lethal effect of the individual compounds.

PUBLICATIONS US Army Center for Health Promotion and Preventive Medicine Report. Acute Oral Toxicity Study of Pyridostigmine Bromide, Permethrin, and DEET in the Laboratory Rat. Toxicological Study 75-48-2665, 31 May 1995.

Title Male/Female Differential Tolerances to Pyridostigmine Bromide

Research Focus: Pyridostigmine Bromide **Research Type:** Clinical Research

Agency DoD **Study Location** Ft. Detrick

Study Start Date 10/1/94 **Estimated Completion Date** 2/1/97

Project Status Ongoing DoD-11

Summary

OVERALL PROJECT OBJECTIVE: To determine if males and females have different tolerances to doctrinal dose (30 mg every 8 hours) of pyridostigmine bromide.
SPECIFIC AIMS: To evaluate the tolerance of pyridostigmine bromide (30 mg every 8 hours for 21 days); to evaluate multiple dose kinetics; and to evaluate the effect of weight in males and females upon drug tolerance.
METHODOLOGY: Double-blind study.
EXPECTED PRODUCTS (MILESTONES): Final Report.
STATUS/RESULTS TO DATE: In life portion of the study and the one year follow-up have been completed. The draft report for the in life portion of the study is under review. Preliminary results from this study indicate that pyridostigmine continues to be safe. Expected side effects, primarily gastrointestinal, were observed. Other events did not appear to be related to the drug since the reporting incidence was equal in active drug and placebo groups. No difference in side effects were found related to gender, size, or weight. Draft report has been peer reviewed and the final report is due by December 1996.

PUBLICATIONS none to date

Title Forward Deployable Diagnostics for Infectious Diseases

Research Focus: Miscellaneous **Research Type:** Applied Research

Agency DoD **Study Location** Ft. Detrick

Study Start Date 10/1/93 **Estimated Completion Date** 9/30/01

Project Status Ongoing DoD-12

Summary

OVERALL PROJECT OBJECTIVE: To develop a series of simple diagnostic assays suitable for forward deployed preventive medicine teams, Area Medical, and Forward Laboratories.
SPECIFIC AIMS: To develop rapid and simple diagnostic tests to permit the identification of the causes of infection outbreaks before they reach the epidemic state. Serological assays are being developed for typhus fever, dysenteries caused by shigella and other bacteria, and leptospirosis. Tests utilizing polymerase chain reaction (PCR) technology are being explored for diagnosing dengue fever. Fluroescent assays for malaria and other parasitic diseases are under investigation. Hand-held chromatographic immunoassays are being developed for dengue fever. Future applications include campylobacter, malaria, and arboviral and rickettsial disease agents. Dipstick technology is being developed for dengue fever as well as rickettsial disease agents responsible for scrub and endemic typhus, and spotted fever roup diseases.
METHODOLOGY: Hand-held chromatographic immunoassays; electrochemiluminescence (ECL) detection; polymerase chain reaction assays; dip-stick assays.
EXPECTED PRODUCTS (MILESTONES): Forward deployable assays using immunochemical - based assays against dengue, hanta-, and selected hemorrhagic fever viruses are expected to reach Milestone I in 4QFY97. Confirmatory polymerase chain reaction assays with high specificity and sensitivity are expected to reach Milestone I in 4QFY98. Field evaluations of selected dip-stick assays will occur during FY96.
STATUS/RESULTS TO DATE: Sensitive and specific enzyme-linked immunoassays are currently available for the detection of selected antigens, or anti-agent IgG/IgM antibodies for a select group of infectious diseases. Application of chromatographic assay technology is expected to occur in FY96 with completed products available by FY98. Prototype polymerase chain reaction assays are currently available for dengue virus and hantaviruses. New PCR technology that will allow automated detection is currently being explored. Evaluation of fieldable reagents and validation of the assays will continue at least until FY98. Initial laboratory development is completed for dip-stick assays for scrub and endemic typhus; dip-sticks for rickettsial spotted fever group and dengue fever disease agents are in progress, and should be completed in FY97; field evaluations follow laboratory development. Laboratory development is in progress for hand-held immunoassays for dengue fever viruses.

PUBLICATIONS

Kelly DJ, Chan CT, Paxton H, Thompson K, Howard R, Dasch GA. Comparative evaluation of a commercial enzyme immunoassay for the detection of human antibody to Rickettsia typhi. Clinical & Diagnostic Laboratory Immunology 2(3):356-60, 1995.

Weddle JR, Chan TC, Thompson K, Paxton H, Kelly DJ, Dasch GA, Strickman D. Effectiveness of a dot-blot immunoassay of anti-Rickettsia tsutsugamushi antibodies for serologic analysis of scrub typhus. Am J Tropical Med & Hygiene, 53(1):43-6, 1995.

Title Effects of Persian Gulf War Service on Military Working Dogs

Research Focus: Miscellaneous
Research Type: Epidemiology Research
Agency DoD
Study Location Ft. Detrick
Study Start Date 4/1/94
Estimated Completion Date 12/1/98
Project Status Ongoing
DoD-13

Summary

OVERALL PROJECT OBJECTIVE: The possibility of exposure to environmental factors and endemic diseases exists for the population of military working dogs (MWDs) that deployed to the Persian Gulf (PG) theater of war. The hypothesis to be tested is that there will be no differences in pathologic diagnoses between the PG MWD cohort and a matched (on basis of age, sex, and breed) comparison group never deployed to Southwest Asia (SWA).
SPECIFIC AIMS: The (null) hypothesis to be tested is that in the final analysis there will be no differences in diagnoses between the PG MWD cohort and the comparison group which never deployed to SWA. Should this hypothesis not be supported: 1) the possiblity exists that differences in pathologic diagnoses between the two cohorts may be the result of deployment to SWA; and 2) dates of deployment and location in theater will be compared among the PG MWDs, and conceivably to those of PG veterans.
METHODOLOGY: The PG MWD cohort was identified after the cessation of hostilities and subsequent redeployment. The inclusive deployment dates for this population are 31 July 1990 to 31 December 1991. Generation of data: Those MWDS still living receive semi-annual physical examinations which include routine panels of hematologic, serologic, and chemical analyses; the results of which are posted in their medical records. Those MWDs identified for this study that are euthanized for medical reasons have peripheral blood samples collected for routine blood tests; results of which are included in the dogs permanent medical record. Medical records from all deceased MWDs in the Department of Defense are archived at the DOD Military Working Dog Veterinary Services (DODMWDVS), Lackland Air Force Base, Texas. Those PG cohort MWDs that have been categorized as "not fit for duty" and not humanely euthanized for extenuating medical reasons, may be relocated to the DODMWDVS kennels facilities where the dog will be allowed to live out its natural life span or until a point when euthanasia is elected to prevent or terminate undue suffering. PG cohort MWDs and the comparison group MWDs will undergo a thorough autopsy upon natural death or euthanasia. At autopsy, gross changes are described, and an extensive set of tissues collected and forwarded to the Department of Veterinary Pathology, the Armed Forces Institute of Pathology (AFIP), Washington, DC. The fixed tissues are processed for histologic examination resulting in a final pathology report; the remaining wet tissues, microslides, and case folder materials are archived. Additional fresh tissue specimens of liver, kidney, lung, and adipose tissue are rapidly frozen at the time of autopsy and eventually forwarded to the AFIP for storage until toxicologic analytic procedures may be performed. Antemortem serum samples from all MWDs are banked at the Regional Laboratory, Fort Sam Houston, Texas. Epidemiologic analysis of all data will be accomplished utilizing a master of public health/epidemiology graduate student and a database management system incorporating SNOMED International software coding terminology.
EXPECTED PRODUCTS (MILESTONES): See Objectives.
STATUS/RESULTS TO DATE: Ongoing. We have identified one hundred twenty-four MWDs that deployed to various locations in the PG theater in support of operations within the inclusive dates listed above. The AFIP (American Registry of Pathology) funded a pilot protocol enabling the early implementation of a database system which includes pathologic (including surgical and postmortem morphologic changes), demographic, regional, temporal and clinical findings from initially identified PG MWD cohort and matched comparison MWDs. The pilot protocol funding expired in 1995.
The collection and epidemiologic analysis of all available data is the primary responsibility of a US Army Veterinary Corps Officer currently enrolled in a master's of public health/epidemiology

graduate study program. The project currently has retained the services of a database management systems consultant with expertise in SNOMED International who will follow the development of the DBMS to completion. This DBMS will operate in FOXPRO with an integration of SNOMED, and is expected to be complete in February 1997.

PUBLICATIONS none to date

Title Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 10/1/93

Estimated Completion Date 9/1/96

Project Status Ongoing

DoD-14

Summary

OVERALL PROJECT OBJECTIVE: Determine the presence of unique characteristics (demographics, aptitude test scores, self-reported health behaviors, past hospitalizations) of Army personnel enrolled in the DVA Registry of Persian Gulf veterans.
SPECIFIC AIMS: The two specific aims of the study are: (1) Investigate logistical, epidemiological, and statistical methodologies for obtaining, combining, and analyzing records. These techniques will be needed for future studies on reported post-deployment illnesses in soldiers who served in the PGW. These techniques would also be applicable in evaluating the health effects of future deployments. (2) Determine which characteristics (to include demographics, past medical history, and health risk behaviors) of soldiers who have been enrolled in the VA PGW registry differ from those who have not enrolled. Ultimately, this information can be used to identify soldiers at a high-risk of reporting post deployment medical problems. These soldiers may be targeted for interventions before or after their deployment to reduce the risk adverse health effects attributable to service in a war zone.
METHODOLOGY: Using case-control methodology we will determine if there is an association between PGW veterans' various demographic, medical, or health behavior characteristics and their probability of enrolling in the PGW registry. Individuals on the VA database and controls from the Defense Manpower Data Center's (DMDC) roster of PGW participants will be the study population. Characteristics evaluated in this hypotheses generating study include demographic factors, recruit applicant aptitude test scores, pre-deployment self-reported health behaviors, and pre-deployment health care utilization as are represented by hospitalizations in military hospitals. These data are available in already existing Army or DoD databases, however, all data may not be available for all study subjects.
EXPECTED PRODUCTS (MILESTONES): (1) A data base of US Army PGW veterans, which includes health indicators and demographic data from the pre, during, and post deployment phases of their military careers. (2) A determination of whether existing data sources can be used to predict a soldier's likelihood of having significant post-deployment adverse health outcomes or a high level of concern about potential health effects of the deployment. This finding will be reported to the military and civilian medical and scientific communities.
STATUS/RESULTS TO DATE: Ongoing. As of March 5, 1996, all databases have been merged and data analysis is underway. Preliminary results should be available within a few months.

PUBLICATIONS none to date

Title Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm

Research Focus: Mortality
Research Type: Epidemiology Research
Agency DoD
Study Location Ft. Detrick
Study Start Date 5/1/94
Estimated Completion Date 1/1/95
Project Status Completed
DoD-15

Summary

OVERALL PROJECT OBJECTIVE: Characterize the disease and non-battle injury (DNBI) mortality experience of US military personnel during ODS/DS. Determine whether US military personnel deployed to Southwest Asia (SWA) had a higher rate of death than US military personnel who did not deploy.
SPECIFIC AIMS: See above objectives.
METHODOLOGY: Casualty reports were used to calculate cause-specific mortality rates among all personnel on active duty in the US Armed Forces (including Reserve and National Guard) over a one-year interval that included the Persian Gulf War. Death rates among active duty personnel deployed to SWA at any time during this period were compared to rates for all military personnel on active duty but not deployed to SWA.
EXPECTED PRODUCTS (MILESTONES): Determination of whether US military personnel deployed to SWA had a higher death rate than non-deployed military personnel.
STATUS/RESULTS TO DATE: Completed. Except for hostile action deaths, the overall mortality experience among US military personnel who deployed to SWA did not significantly differ from that observed among US military personnel who did not deploy to SWA. No evidence of clusters of unexpected deaths were found, except for two accidents. Each death was characterized as to have been most liekly caused by disease or trauma. Trauma deaths were additionally classified as due to unintentional (accidental) injury, battle injury, self-inflicted injury, or homicide.

PUBLICATIONS

Walter Reed army Institute of Research Report. Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm. January 1995.

Writer JV, DeFraites RF, Brundage JF. Comparative mortality among US military personnel in the Persian Gulf region and worldwide during Operations Desert Shield and Desert Storm. JAMA; 275(2):118-121, 1996.

Title Kuwait Oil Fire Health Risk Assessment

Research Focus: Environmental Toxicology

Research Type: Applied Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 5/5/91

Estimated Completion Date 2/18/94

Project Status Complete

DoD-16

Summary

OVERALL PROJECT OBJECTIVE: To characterize both the carcinogenic and noncarcinogenic health risks to DOD troops and civilian employees exposed to the environment affected by the oil fires during and after Operation Desert Storm.
SPECIFIC AIMS: 1. Environmental Monitoring. The environmental monitoring study attempted to characterize the concentration of pollutants that DOD personnel were exposed to during their deployment in the Gulf region. Air monitoring and soil sampling data were used to calculate exposure point concentrations for individual Health Risk Assessments in the final report. 2. Industrial Hygiene Sampling Study. The industrial hygiene air survey monitored and characterized occupational exposures of DOD personnel who had potential high risk exposure to oil fire emissions. The focus was on individuals working outdoors and on worst-case situations within the oil fields next to Kuwait City. 3. Biological Surveillance Initiative. The Biological Surveillance Initiative was conducted to refine and corroborate the results from the Health Risk Assessment. This was accomplished by a collection of objective biological measurements of exposure and effect in real-time, and by establishment of any observable biologic effect or marker of exposure to oil fire pollutants in a cohort of U.S. soldiers.
METHODOLOGY: 1. Sampling and Analysis. Sampling and analytical methodologies for ambient air, soil, industrial hygiene air, biologic samples, and quality assurance procedures are detailed in the final report. 2. Risk Assessment. The methodology used for this Health Risk Assessment was the EPA guidance for the Comprehensive Environmental Response, Compensation and Liability Act sites (CERCLA), also known as "Superfund" sites. The methodology did not determine an individual's health outcome or include the use of reported health effects data. The components of the risk assessment process included data collection and evaluation, exposure assessment, toxicity assessment, and risk characterization and uncertainty analysis.
EXPECTED PRODUCTS (MILESTONES): Reports
STATUS/RESULTS TO DATE: Completed. The potential for significant long-term adverse health effects for the exposed DOD troop or civilian employee populations is minimal. The total predicted excess carcinogenic risk both in Kuwait and in Saudi Arabia did not exceed 3 excess cancers per 1,000,000 population exposed. The predicted carcinogenic risk levels are well within the EPA range of acceptable excess carcinogenic risks. The majority (>99%) of noncarcinogenic risk at all monitoring sites is predicted to be from the inhalation of volatile organic compounds and is assessed as low. The results of the Biological Surveillance Initiative support the conclusion that noncarcinogenic risk levels indicate minimal potential adverse health effects.

PUBLICATIONS US Army Environmental Hygiene Agency, Final Report. Kuwait Oil Fire Health Risk Assessment. No. 39-26-L192-91, 18 February 1994.

Title Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning

Research Focus: Pyridostigmine Bromide
Research Type: Epidemiology Research
Agency DoD
Study Location Ft. Detrick
Study Start Date 1/1/91
Estimated Completion Date 5/21/92
Project Status Complete
DoD-17

Summary

OVERALL PROJECT OBJECTIVE: To obtain safety data for New Drug Application with the Food and Drug Administration (FDA).
SPECIFIC AIMS: To perform retrospective evaluation of effects of pyridostigmine use in the Persian Gulf.
METHODOLOGY: Retrospective evaluation.
EXPECTED PRODUCTS (MILESTONES): Reports.
STATUS/RESULTS TO DATE: Complete. Three surveys were completed, reports prepared, and forwarded to the FDA. Results indicated that pyridsotigmine continues to be safe. Side effects reported were primarily gastrointestinal in nature. Headaches were also reported by the respondents.

PUBLICATIONS Three Survey Reports consolidated Into an Amendment to the FDA IND Application

Title Kuwait Oil Fires Troop Exposure Assessment Model (TEAM)

Research Focus: Environmental Toxicology

Research Type: Applied Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 5/31/93

Estimated Completion Date 12/31/96

Project Status Complete

DoD-18

Summary

OVERALL PROJECT OBJECTIVE: To respond to Public Law 102-190 (Section 734: Troop Registry from exposure to oil well fires in Operation Desert Storm) by characterizing the potential carcinogenic and non-carcinogenic health risks to U.S. military personnel exposed to the environment affected by the oil well fires during and after Operation Desert Storm.
SPECIFIC AIMS: The site-specific Kuwait Oil Fire Health Risk Assessment addressed the risks to DOD troops located at the eight fixed air/soil sampling sites where actual environmental data were collected and anlyzed. This study will incorporate actual site data with the modeled air concentrations, exposure data, and the Troop Location Registry data, to determine the risk to U.S. military personnel that were not located at fixed sampling sites for their entry tour of duty and for periods of time when no sampling occurred.
METHODOLOGY: Using a geographic information system (GIS) that is capable of mapping troop location and movement over time, in conjunction with the troop movement database, the locations of all US military personnel are being mapped during Operation Desert Storm. Once troop locations have been determined and mapped, the GIS determines troop exposure to oil fire pollution using satellite images, modeled plume boundaries, oil field crude composition data, oil field emission rates, modeled pollutant concentrations, and actual field data. When troop location and exposure have been determined, the potential health risks resulting from the exposure will be determined.
EXPECTED PRODUCTS (MILESTONES): The outcomes expected from this study will be the determination of exposure and potential health risks associated with oil fire pollution for U.S. military personnel participating in Operation Desert Storm.
STATUS/RESULTS TO DATE: This project is ongoing. A majority of the data have been entered into the system. Both satellite plume and modeled plume boundaries (over 270 days, or the February - October 1991 timeframe) have been digitized. Pollutant-specific oil fire emission factors have been derived and integrated into the TEAM; updates on these are on-going. Complete unit identification code location data for the Navy, Marine Corps and Air Force (over 134,000 records) have been entered into the TEAM database. Over 195,000 Army UIC location data are in the TEAM database. The Army UIC location data are incomplete; we expect the final Army UIC location data to be entered into the TEAM database on/about July 26, 1996. In addtion, the Desert Storm personnel roster (over 757,000 individuals) are in the TEAM database. We are currently updating the toxicological (from IRIS and HEAST databases) and exposure factor tables of the TEAM database. Over 2,000,000 records have been entered into the TEAM database.

PUBLICATIONS US Army Environmental Hygiene Agency, Final Report. Kuwait Oil Fire Health Risk Assessment. No. 39-26-L192-91, 18 Feb 1994. This report describes the eight fixed air/soil sampling sites study and presents the preliminary results of the KOFTEAM pilot project.

Title Persian Gulf Veterans Health Tracking System

Research Focus: Environmental Toxicology

Research Type: Applied Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 4/1/96

Estimated Completion Date 12/31/97

Project Status Ongoing

DoD-19

Summary

OVERALL PROJECT OBJECTIVE: To respond to Public Law 102-585 (Section 702: Scientific research using Troop Health Registry) by characterizing all potential exposures (e.g., oil fires, vaccines, chemical/biological warfare agents, pesticides, pyridostigmine bromide, etc) to U.S. military personnel participating in Operation Desert Storm, and to assess the potential health consequences of those exposures.
SPECIFIC AIMS: The site-specific Kuwait Oil Fire Health Risk Assessment and the Troop Exposure Assessment Model (TEAM) address the potential risks to U.S. military personnel from potential exposure to airborn contaminants from oil well fires. This study attempts to characterize other potential exposures experienced by U.S. military personnel during Operation Desert Storm and to assess the potential health risks/consequences of those potential exposures.
METHODOLOGY: The Persian Gulf Veterans Health Tracking System uses a geographical information system (GIS) to assess potential exposures and medical outcomes for U.S. military personnel who participated in Operation Desert Storm. Once troop locations are determined and mapped (from the Troop Location Registry data), the GIS can help determine potential troop exposure to any number of different chemicals, environmental threats, or other materials. When troop locations and potential exposures have been determined, the potential health risks resulting from the potential exposures can be determined. In additon to examining potential exposure, databases on medical outcomes (e.g., Comprehensive Clinical Evaluation Program, the Veterans Administration Mortality Study, etc.) can be evaluated by studying potential exposures, locations, movements, and relationships of the troops in these databases for epidemiological significance.
EXPECTED PRODUCTS (MILESTONES): Characterization of the potential exposures and health risks/outcomes associated with service by U.S. military personnel in Operation Desert Storm.
STATUS/RESULTS TO DATE: Ongoing. The CCEP database has been integrated into the GIS. Space and time analyses are being performed on the possible low-level chemical agent exposure from munition storage bunker detonations to include the Tall Al Lahm, Hafir Al Batin, and other sites. The soldiers and Units identified in the CCEP, the Environmental Support Group troop unit movement database, and the Defense Manpower Data Center Operation Desert Storm personnel roster are being mapped with respect to their proximity to these sites. Exposure analyses are being performed with dispersion modeling results from the Central Intelligence Agency. We are planning to integrate the chemical detection network data into the GIS for additional low-level chemical agent analyses. In addition, other environmental exposure data sets/databases to include scud sites, tent heaters, microwaves, and dust suppression are being collected and assessed. The CHPPM is expecting to finalize the project database status and methodologies by September 1996.

PUBLICATIONS none to date

Title A Statistical Study Correlating the Reported Cases of Gulf War Syndrome to Battlefield Locations of Afflicted US Army Personnel During the Iraq-Kuwait War; Part 1: Method to Related Troop Deployment and the Reported Cases of Gulf War Syndrome and Probable Incidence of Maladies Defined by ICD-9-CM

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 1/1/94

Estimated Completion Date 7/1/95

Project Status Complete

DoD-20

Summary

OVERALL PROJECT OBJECTIVE: To devise a procedure for counting the collections of symptoms and diagnoses of veterans' illnesses and relating them to the U.S. military grid system locations in the Kuwait-Iraq-Saudi Arabian theater of operations.
SPECIFIC AIMS: To identify the geographic locations by date of the Army personnel who served in the Gulf War and whose names are recorded in the VA register as experiencing severe health problems. The units to which these personnel were assigned are tracked across the Iraq-Kuwait region, in order to determine whether epidemiological commonalities can be detected based upon location at certain dates.
METHODOLOGY: VA malady codes of afflicted personnel related to unit identification codes were identified. Malady information was regrouped and coded into crip and fuzzy numbers. For the Part 1, only crisp numbered malady information was used. The DOD Register was used to identify geographic coordinate locations of Army units. A mathematical algorithm was developed to compare geographic location to maladies and possible cause(s) of each of the maladies. The algorithm is based on the ratios of the number of combatants reporting illnesses (in any grid) to the total number of combatants (occupying the grid) as discrete probabilities. These are considered to be the probabilities of occurrence of a health condition for the total time period that a military unit occupies a grid. A production model needs to be completed to compute statistical measures that are concerned with Gulf War veterans' illnesses.
EXPECTED PRODUCTS (MILESTONES): A mathematical procedure to count the collections of symptoms and diagnoses over the various map grids of the region.
STATUS/RESULTS TO DATE: Completed.

PUBLICATIONS Army Research Laboratory Technical Report ARL-TR-800, July 1995.

Title Study of Variability In Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals With Symptoms Following Participation in Operation Desert Storm

Research Focus: Pyridostigmine Bromide **Research Type:** Epidemiology Research

Agency DoD **Study Location** Walter Reed Army MC

Study Start Date 7/11/95 **Estimated Completion Date** 6/30/97

Project Status Ongoing DoD-21

Summary

OVERALL PROJECT OBJECTIVE: To determine if individuals have different sensitivities to inhibition of blood cholinesterases by pyridostigmine and/or differences in the rate of spontaneous reactivation of cholinesterases after pyridostigmine exposure. To determine if there is a difference in the cholinesterases of Gulf War veterans who took pyridostigmine and seen at the Gulf War Health Center compared to age and sex matched controls.
METHODOLOGY: Blood (in EDTA) is obtained from Gulf War veterans seen at the Gulf War Health Center at Walter Reed Army Medical Center and from age and sex matched controls. The blood samples are sent to the laboratory at Walter Reed Army Institute of Research (WRAIR) in a blinded fashion. At WRAIR, acetylcholinesterase and butrylcholinesterase activity is measured. The reactivation time of the enzymes after in vitro exposure to pyridostigmine is also measured.
EXPECTED PRODUCTS (MILESTONES): June 96 Initial results of first 40 volunteers; June 97 Results of 100 volunteers.
STATUS/RESULTS TO DATE: After the blood of the first 20 controls and 20 Gulf War veterans were evaluated by the laboratory, these specimens were unblinded and analyzed. Mean whole blood lysate acetylcholinesterase concentration for all subjects were 5.7 U/ml; mean plasma butrylcholinesterase concentration was 4.9 U/ml. There was no statistical difference between the controls and the veterans. Reactivation time (t-1/2 at 5 micromolar pyridostigmine) for all subjects ranged from 29.0 to 45.2 minutes with a mean of 37.0. Mean for veterans and controls were 38.4 and 35.9 minutes, respectively. There was no statistically significant difference between the two groups. As of August 1996, 71 volunteers have entered the study.
In the initial small cohort of volunteers, there was no difference between the enzymatic activity of acetylcholinesterase or butrylcholinesterase in controls or veterans. There was no difference between the two groups in the reactivation time after in vitro exposure of the blood to pyridostigmine.

PUBLICATIONS In vitro pyridostigmine inhibition of red cell acetylcholinesterase: a comparison in Gulf war veterans and normal controls. 1996 Medical Defense Bioscience Review, Baltimore, Maryland.

Title A Statistical Study Correlating the Reported Cases of Gulf War Syndrome to Battlefield Locations of Afflicted US Army Personnel During the Iraq-Kuwait War; Part 1: Method to Related Troop Deployment and the Reported Cases of Gulf War Syndrome and Probable Incidence of Maladies Defined by ICD-9-CM

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 1/1/94

Estimated Completion Date 7/1/95

Project Status Complete

DoD-20

Summary

OVERALL PROJECT OBJECTIVE: To devise a procedure for counting the collections of symptoms and diagnoses of veterans' illnesses and relating them to the U.S. military grid system locations in the Kuwait-Iraq-Saudi Arabian theater of operations.
SPECIFIC AIMS: To identify the geographic locations by date of the Army personnel who served in the Gulf War and whose names are recorded in the VA register as experiencing severe health problems. The units to which these personnel were assigned are tracked across the Iraq-Kuwait region, in order to determine whether epidemiological commonalities can be detected based upon location at certain dates.
METHODOLOGY: VA malady codes of afflicted personnel related to unit identification codes were identified. Malady information was regrouped and coded into crip and fuzzy numbers. For the Part 1, only crisp numbered malady information was used. The DOD Register was used to identify geographic coordinate locations of Army units. A mathematical algorithm was developed to compare geographic location to maladies and possible cause(s) of each of the maladies. The algorithm is based on the ratios of the number of combatants reporting illnesses (in any grid) to the total number of combatants (occupying the grid) as discrete probabilities. These are considered to be the probabilities of occurrence of a health condition for the total time period that a military unit occupies a grid. A production model needs to be completed to compute statistical measures that are concerned with Gulf War veterans' illnesses.
EXPECTED PRODUCTS (MILESTONES): A mathematical procedure to count the collections of symptoms and diagnoses over the various map grids of the region.
STATUS/RESULTS TO DATE: Completed.

PUBLICATIONS Army Research Laboratory Technical Report ARL-TR-800, July 1995.

Title Study of Variability In Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals With Symptoms Following Participation in Operation Desert Storm

Research Focus: Pyridostigmine Bromide **Research Type:** Epidemiology Research

Agency DoD **Study Location** Walter Reed Army MC

Study Start Date 7/11/95 **Estimated Completion Date** 6/30/97

Project Status Ongoing DoD-21

Summary

OVERALL PROJECT OBJECTIVE: To determine if individuals have different sensitivities to inhibition of blood cholinesterases by pyridostigmine and/or differences in the rate of spontaneous reactivation of cholinesterases after pyridostigmine exposure. To determine if there is a difference in the cholinesterases of Gulf War veterans who took pyridostigmine and seen at the Gulf War Health Center compared to age and sex matched controls.
METHODOLOGY: Blood (in EDTA) is obtained from Gulf War veterans seen at the Gulf War Health Center at Walter Reed Army Medical Center and from age and sex matched controls. The blood samples are sent to the laboratory at Walter Reed Army Institute of Research (WRAIR) in a blinded fashion. At WRAIR, acetylcholinesterase and butrylcholinesterase activity is measured. The reactivation time of the enzymes after in vitro exposure to pyridostigmine is also measured.
EXPECTED PRODUCTS (MILESTONES): June 96 Initial results of first 40 volunteers; June 97 Results of 100 volunteers.
STATUS/RESULTS TO DATE: After the blood of the first 20 controls and 20 Gulf War veterans were evaluated by the laboratory, these specimens were unblinded and analyzed. Mean whole blood lysate acetylcholinesterase concentration for all subjects were 5.7 U/ml; mean plasma butrylcholinesterase concentration was 4.9 U/ml. There was no statistical difference between the controls and the veterans. Reactivation time (t-1/2 at 5 micromolar pyridostigmine) for all subjects ranged from 29.0 to 45.2 minutes with a mean of 37.0. Mean for veterans and controls were 38.4 and 35.9 minutes, respectively. There was no statistically significant difference between the two groups. As of August 1996, 71 volunteers have entered the study.
In the initial small cohort of volunteers, there was no difference between the enzymatic activity of acetylcholinesterase or butrylcholinesterase in controls or veterans. There was no difference between the two groups in the reactivation time after in vitro exposure of the blood to pyridostigmine.

PUBLICATIONS In vitro pyridostigmine inhibition of red cell acetylcholinesterase: a comparison in Gulf war veterans and normal controls. 1996 Medical Defense Bioscience Review, Baltimore, Maryland.

Title Chronic Organophosphorus Exposure and Cognition

Research Focus: Environmental Toxicology

Research Type: Basic Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 4/15/95

Estimated Completion Date 5/14/98

Project Status Ongoing

DoD-22

Summary

OVERALL PROJECT OBJECTIVE: This study will evaluate the effects of low-level sub-chronic exposure to an organophosphorus cholinesterase inhibitor on normal cognitive function in animal models. The long term goals are to identify the underlying mechanisms of organic brain damage related to environmental toxins and to develop novel treatment strategies to improve memory/cognitive performance in affected patients.
SPECIFIC AIMS: 1. Does low-level sub-chronic exposure to an organosphorus (OP) cholinesterase inhibitor produce learning or memory deficits in rats and non-human primates trained to perform varios memory tasks; and will prior exposure to atropine sensitize animals to atropine sensitize animals to OP agents? 2. Is memory impairment to an OP agent associated with alterations in the presynaptic regulation of cholinergic neurons in relevant brain regions in rats; and/or is there an alteration in the ability of the brain adrenergic system to regulate presynaptic cholinergic function? 3. Is memory impairment to an OP agent associated with alterations in the postsynaptic regulation of cholinergic or adrenergic receptors? Can these alterations be reflected in the genes encoding the various muscarinic or nicotinic receptor subtypes? 4. Can new therapies (reversible cholinesterase inhibitors, nicotinic agonists, adrenergic agonists) which improve memory deficits in Alzheimer's patients also improve cognitive function in rats or monkeys with OP-induced memory impairment?
METHODOLOGY: Protocol 1. Three groups of 12 rats each will be administered 0.25, 0.5, or 1.0 mg/kg of DFP once daily over 2 weeks. The status of brain muscarinic receptors and blood cholinesterase will be determined and 2 days after the last dose of DFP they will be examined for performance in the Morris water mase. Monkeys will be well-trained in the delayed matching-to-sample (DMTS) task. The highest dose of DFP which does not elicit overt signs of anticholinesterase toxicity or which will not decrease DMTS performance will be employed in the study. Protocol 2. Rats will be administered a 14-day DFP regimen. Samples of regional brain tissue will be taken on 4 occasions during treatment from randomly selected rats (6 per time point) to determine the status of choline acetyl transferase (ChAT) activity and for the estimation of ACh turnover rates. We will examine the ability of clonidine to inhibit presynaptic cholinergic function using biochemical techniques. Finally, these experiments will be repeated in rats subjected to atropine sensitization. Protocol 3. Rats will be administered a 14-day DFP regimen. Samples of regional brain tissue will be taken on four occasions during treatment to determine the status of muscarinic, nicotinic, and alpha-adregenic receptor subtypes in several brain regions using quantitative receptor autoradiography. Small samples of tissue will be removed for quantitative RT-PCR. Protocol 4. The monkeys which have been evaluated in Protocol 1 for production of long-term decrements in DMTS performance will be employed. They will receive increasing doses of drugs designed to enhance cognitive performance. The experiments will occur concomitantly with a similar series performed in rats tested using the Morris water maze.
EXPECTED PRODUCTS (MILESTONES): This research will be dedicated to the elucidation of the mechanism of permanent memory dysfunction produced by exposure to a relevant organophosphorus agent DFP in non-human primate and rat models. Also, we will evaluate the effects of reversing this memory impairment using classical and novel agents developed for patients with alzheimer's disease.
STATUS/RESULTS TO DATE: Chronic, low-level exposure to acetylcholinesterase (Ache) inhibitor organophosphate (OP) insecticides or chemical warfare agents produces abnormalities in CNS

acetylcholine (ACh) function, and in humans, may be associated with impaired cognitive function well after withdrawal form such exposure. The purpose of the present study was to identify the severity of impairment in spatial learning of rats and monkeys following protracted withdrawal form chronic, low-level exposure to the OP agent diisopropylfluorophosphate (DFP). Assessment of spatial learning began either 3 or 17 days after completion of a 14 day DFP treatment regimen (50, 250, or 500 mg/kg). During the 14 day treatment regimen, prior to withdrawal, spontaneous activity and olfactory behaviors were initially suppressed during DFP exposure, effects which became tolerant with repeated exposure to the 250 mg/kg dose regimen. Performance of a standard water maze task was impaired for up to 21 days after withdrawal from treatment with a 250 mg/kg dose of DFP. Latencies to find a hidden platform were increased by 30-40% above control levels throughout testing and no overt signs of DFP toxicity were evident. All animals did, however, demonstrate the ability to eventually learn the task. AChE activity in the frontal cortex and hippocampus was suppressed to 41% and 51% of control levels, respectively, after 14 days of DFP (250 mg/kg) treatment. By 7 days after withdrawal from treatment, frontal cortex AChE activity had recovered to 84% of control levels, whereas hippocampal AChE activity had recovered to only 64.40%. By 21 days after withdrawal form treatment, AChE in both brain regions had recovered to near-control levels. Performance of a previously well-learned delayed matching task by monkeys was not affected by DFP regimens after withdrawal of the drug. Chronic, low-level OP exposure, therefore, produces protracted impairment of working memory after drug withdrawal that is not associated with continue suppression of AChE activity. This impairment may be attributed to the decrease in recovery of AChE in the hippocampus, relative to the cortex. This decreased rate of enzyme recovery may contribute to hippocampal toxicity underlying protracted impairment of working memory. In 3 rhesus monkeys well trained in the performance of a delayed response task, chronic daily exposure to 10-20 mg/kg of DFP produced severe toxicity and task impairment after 8 weeks of treatment. However, task performance was at near control levels by 6-10 days after DFP withdrawal. Withdrawal from chronic exposure to low levels of DFP may compromise working memory or learning of a new task, but fails to inhibit the performance of a well learned task if no toxicity is present.

Celastrus paniculatus (CP), a medicinal plant from India has been reputed to be useful as a pharmaceutical aid for learning and memory. We investigated the effects of the seed oil of CP on the 6 day performance of young adult rats in a navigational memory task. Chronic oral (gavage) daily treatment with CP, (50, 200, or 400 mg/kg) for 14 days completely reversed the scopolamine (0.5 mg/kg)-induced task performance deficit. Acute treatment or chronic 14 day treatment with CP resulted in no significant alteration in normal locomotor activity in an open field. Moreover, CP did not alter the scopolamine-induced increases in horizontal locomotor activity. Chronic treatment with CP did not alter brain acetylcholinesterase levels and no signs of cholinergic overstimulation were ever noted during or after treatment. Thus, the seed oil of CP, when administered chronically, selectively reversed the impairment in spatial memory produced by acute central muscarinic receptor blockage, supporting the possibility that one or more constituents of the oil may offer cognitive enhancing properties. CP may be more effective in individuals who are cognitively impaired as a result of chemical or organic brain damage as compared with normal subjects.

PUBLICATIONS none to date

Title Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families

Research Focus: Brain & Nervous System

Research Type: Epidemiology Research

Agency DoD

Study Location Ft. Detrick

Study Start Date 10/1/93

Estimated Completion Date 9/1/98

Project Status Ongoing

DoD-23

Summary

OVERALL PROJECT OBJECTIVE: Determine the acute and long-term impact of deployment to SWA on the physical and mental health of soldiers and their families.
SPECIFIC AIMS: Determine the acute and long-term impact of deployment to SWA on the physical and mental health of soldiers organizational, and environmental factors within military units that produce psychiatric casualties. Identify the critical indicators resulting in increased risk and assess the long-term consequences of exposure to trauma. Develop recommendations on post-deployment interventions. Determine impacts of Army family support policies and programs on active duty and reserve component soldiers and their families.
METHODOLOGY: Interviews and surveys of soldiers and leaders participating in ODS were conducted several times prior to the ground war, immediately after the ground war, and at intervals following return home. Soldiers and their spouses were surveyed and interviewed in order to evaluate the social, psychological, organizational, and environmental factors within military units that produce psychiatric casualties, lead to dysfunctional behavior and decrements in military performance, generate psychomatic illness and increased susceptibility to physical illness. The family-community research team performed field surveys of spouses of active duty and reserve compenent (USAR) and (ARNG) soldiers from units deployed to the Persian Gulf for ODS on deployment-related stressors and psychological symptoms, spouse support-seeking behavior, family perceptions of Army support and assistance, stress-coping responses, and family well-being during reunion with returning soldiers and in the aftermath of ODS. Surveys and interviews of selected Reserve and National Guard units and their familities have been conducted during the period following ODS, while additional interviews and surveys were conducted with soldiers and families participating in Operation Just Cause and Sinai peacekeeping deployments.
EXPECTED PRODUCTS (MILESTONES): Develop recommendations affecting post-combat interventions. Determine the impact of Army family support policies and programs on both active duty and research component soldiers and families.
STATUS/RESULTS TO DATE: Ongoing. An assessment of phychological factors related to deployment stress and family separation during Operation Desert Shield/Storm was conducted with a stratified sample of married and single U.S. Army Individual Ready Reserve soldiers two years post ODS. Analyses were performed in 1994 with final report completed in spring of 1995. Report submitted to Army Deputy Chief of Staff for Personnel. Deployment stress and adaptation was studied on a large sample of U.S. Army National Guard and U.S. Army Reserve Unit (TPU) soldiers who activated and deployed for Operation Desert Shield/Storm. Physiological stress, distress, coping and factors related to current deployed effects of family separation were assessed. Physiological well-being was studied with respect to deployment location factors. Persian Gulf Region analyses were performed in summer of 1995 and resulted in a manuscript on the long term effects of Desert Storm on the Army Reserve and National Guard soldiers and their families.

PUBLICATIONS

Epidemiological considerations regarding the health and effectiveness of women in the armed forces. Technical Report, AD#ADA278202.

Combat service support survey results: A light infantry division and a mechanized infantry division. Technical Report AD#ADA278203.

The Long Term Effects of Operation Desert Storm on the Psychological Well-Being of US Army Reserve and National Guard Veterans. Manuscript under

review by editors of J Applied Social Psychology.

Title Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency DoD

Study Location Washington

Study Start Date 6/1/96

Estimated Completion Date 1/31/99

Project Status Ongoing

DoD-30

Summary

OVERALL PROJECT OBJECTIVE: This research addresses the effects of Gulf War service on military women's health. The studies will compare the incidence, prevalence, general health outcomes, and risks of women deployed in the Gulf War theater of operations with Gulf War era women who were not deployed to the Gulf.
SPECIFIC AIMS: Linkage of exposure to outcomes. Health outcomes of women who served in the Persian Gulf War.
METHODOLOGY: Self-reported survey linked to Persian Gulf tracking file and other mapping files.
EXPECTED PRODUCTS (MILESTONES): Reports and publications.
STATUS/RESULTS TO DATE: Ongoing. Questionnaires to OMB in late fall of 1996. Met with Director U.S. Army and Joint Services Environmental Support Group.

PUBLICATIONS none to date

Title Dysregulation of the Stress Response in the Persian Gulf Syndrome

Research Focus: Brain & Nervous System

Research Type: Epidemiology/Clinical Research

Agency DoD

Study Location Washington, DC

Study Start Date 5/6/96

Estimated Completion Date 6/6/99

Project Status Ongoing

DoD-31

Summary

OVERALL PROJECT OBJECTIVE: The purpose of this study is to demonstrate that objective neurohormonal abnormalities in the human 'stress response' are present in Gulf War veterans with unexplained multiple symptoms similar to fibromyalgia, chronic fatigue syndrome, somatoform disorder, multiple chemical sensitivity and that these neurohormonal abnormalities are at least partly responsible for these symptoms. There are several axes of the stress response which can independently or concurrently function aberrantly in these conditions, including the autonomic nervous system, the hypothalamic-pituitary axes, and descending anti-nociceptive pathways. Specific symptomatology results when each of these systems functions improperly.
SPECIFIC AIMS: In this study the investigators propose to demonstrate that:
a. Gulf War veterans with undiagnosed symptoms display centrally mediated disturbances in autonomic tone, and this leads to vasomotor instability and smooth muscle dysmotility, and symptoms such as irritable bowel syndrome, and migraine headaches.
b. Gulf War veterans with undiagnosed symptoms display diffuse disturbances in nociception (pain threshold) that are partly responsible for many of the pain-related symptoms seen in this condition (e.g., myalgia, arthralgia, sore throat).
c. The same neuroendocrine changes seen in fibromyalgia, chronic fatigue syndrome, and post-traumatic stress syndrome, characterized by blunting of the hypothalamic-pituitary axes, are seen in Gulf War veterans with undiagnosed symptoms, and contribute substantially to the fatigue seen in this condition.
METHODS: Each of these hypotheses will be tested in a multidisciplinary study which involves a collaborative effort between Georgetown Unviersity Medical Center, the Washington D.C. VA Medical Center (a specialized care center for Gulf War veterans) and consultants from the National Institutes of Health. The demonstration of common underlying pathophysiologic mechanisms in fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity and the undiagnosed illnesses of Gulf War veterans will be tremendously beneficial. This research should lead to both more effective treatment of these individuals and perhaps effective strategies to avoid these problems in future deployments.
EXPECTED PRODUCTS (MILESTONES):
STATUS/RESULTS TO DATE:

PUBLICATIONS none to date

Title Neuropsychological Functioning in Persian Gulf Era Veterans

Research Focus: Brain & Nervous System

Research Type: Epidemiology/Clinical Research

Agency DoD

Study Location VAMC Boston, MA

Study Start Date 5/1/96

Estimated Completion Date 5/1/99

Project Status Ongoing

DoD-32

Summary

OVERALL PROJECT OBJECTIVE: To evaluate the neuropsychological functioning of PGW-era veterans who are seeking treatment or diagnostic evaluation for any type of health or adjustment complaint. The group of patients who were deployed to the Gulf are being compared to a treatment seeking patient group who were not deployed to the Gulf. Data from these groups are also being compared with those from a (non-treatment seeking) research sample of PGW veterans who are being studied using the same neuropsychological instruments. In addition, all of these patients and research subjects are being administered a standardized set of questionnaires and semi-structured interviews that will identify their current health symptoms, pre-existing physical and mental health condition, sociodemographic variables, Gulf experiences, and Post PGW-era stressors. These instruments also permit PTSD, MCS, CFS, and other psychiatric disorders to be diagnosed.
SPECIFIC AIMS: The specific aim of this study is to determine whether veterans of the Persian Gulf War (PGW) show cognitive impairments suggestive of central nervous system damage at a greater rate than PGW-era veterans who were not deployed to the Gulf.
METHODOLOGY: Two hundred subjects will be examined in three years; 100 veterans deployed to the Gulf during the PGW and 100 serving in the military during that era who were not deployed to the Gulf. These subjects will be recruited from among those seeking treatment or diagnostic evaluation at the Boston VAMC through all outpatient treatment services. It is anticipated that approximately 40 subjects in each group will be recruited in each of years 1 and 2, and 20 in each group in year 3 of the proposed period of support. The recruitment procedure has been fully outlined. It has been devised to reduce selection bias that would reduce the comparability of Gulf-deployed and non-deployed veterans.
a. Subjects. All treatment seeking veterans discharged from the military since the beginning of the PGW will be considered potential subjects. A list of veterans who have been admitted to any outpatient clinical service (with the exclusion of the substance abuse clinic) at the Boston VAMC in Jamaica Plain, the outpatient clinic at Causeway Street, and the Lowell VAMC will be generated by the supervisor of outpatient clinics and will be updated periodically. This list will include names, social security numbers, and telephone numbers (where available) or addresses (if telephone numbers are not available). As a preliminary step, the lists will be cross-checked with the Persian Gulf War Registry to determine the approximate proportions of the PGW veterans and non-deployed PGW-era veterans available. However, the personnel involved in the recruitment of subjects will not be aware of the status of potential subjects with regard to deployment to the Gulf and steps will be taken to reduce the likelihood that this information will become known to project staff during the recruitment process.
b. Initial Contact. The first contact with potential subjects will be by telephone (or by mail, if there is no telephone number available). At the beginning of this contact, subjects will be requested to not indicate whether or not they served in the Gulf. They will be told that, if they should decide to participate in the research project, information concerning deployment will be obtained at a later time. The initial contact will consist of a description of the project, including types of assessment, time required, and financial compensation. Subjects will have an opportunity to ask questions about the procedure. They will be informed that whether or not they participate will have no bearing on their medical care and that, if they choose to participate, that they may withdraw at any time without prejudice. They will be asked to indicate whether they wish to participate, wish not to participate, or wish to defer this decision. An appointment at the Boston VAMC will be scheduled for

patients agreeing to participate.
c. Methods. Patients will first be seen for a brief screening interview and patients retained in the study sample will be presented the study consent form for signature. Subjects will complete a battery of neuropsychological tests, a set of questionnaires, and 2 semi-structured interviews (one will encompass their current health and past environmental exposure history; the other will be done to determine psychiatric and/or PTSD diagnoses).
EXPECTED PRODUCTS (MILESTONES): To isolate factors that may differentiate those who served in the Gulf who are seeking treatment for health complaints from their treatment-seeking counterparts who were not deployed to the Gulf. This is a step toward understanding the Gulf War Syndrome.
STATUS/RESULTS TO DATE: Potential subjects have been identified from database of outpatients seeking treatment and subject recruitment is currently proceeding.

PUBLICATIONS none to date

Title Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity

Research Focus: Pyridostigmine Bromide **Research Type:** Basic Research

Agency DoD **Study Location** Chapel Hill, NC

Study Start Date 7/1/96 **Estimated Completion Date** 6/30/98

Project Status Ongoing DoD-33

Summary

OVERALL PROJECT OBJECTIVE: Demonstrate that there are strain differences in the acute effects of pyridostigmine and the ability of chronic pyridostigmine to protect against other anticholinesterase agents.
SPECIFIC AIMS: Determine strain-dependent effects of acute and chronically administered pyridostigmine; determine whether chronic pyridostigmine will protect agonists effects of other anticholinesterase agents.
METHODOLOGY: Rats will be treated with pyridostigmine acutely or chronically and growth hormone, body temperature and locomotor activity will be assessed.
EXPECTED PRODUCTS/MILESTONES: Development of challenge to predict cholinergic sensitivity in soldiers.
STATUS/RESULTS TO DATE: Animals being bred, materials ordered.

PUBLICATIONS none to date

Title Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents

Research Focus: Environmental Toxicology

Research Type: Applied Research

Agency DoD

Study Location Albuquerque, NM

Study Start Date 6/7/96

Estimated Completion Date 7/6/98

Project Status Ongoing

DoD-34

Summary

OVERALL PROJECT OBJECTIVE: To conduct a study that simulates human exposure to aerosols in invented tents heated by leaded diesel fuel, with the tent and fuel composition similar to those used in the Persian Gulf, so that the contribution of exposure to this in-tent pollutant can be estimated.

SPECIFIC AIMS: 1) Physical and chemical characterization of aerosols produced by heaters that burned leaded diesel fuel in an unvented tent; and, 2) Estimation of exposure to lead, combustion gases (such as CO2, CO, NOx, and SO2), and organic compounds (such as PAHs).

METHODOLOGY: The tent and heaters will be obtained from the Army, and four heaters will be evaluated for variability. Aerosols and vapors will be characterized physically and chemically using a Tenax sampler (vapors), the Lovelace Multi-jet Cascade Impactor/Parallel Flow Diffusion Batter (aerosol size distribution, concentration, and chemical composition vs. particle sizes), an electrostatic precipitator sampler (particle morphology), and filter samples (aerosol concentration). These samples will provide chemical compositions, lead content, time-averaged aerosol size distribution, and concentration. Real-time aerosol size distribution and concentration as a function of time will be obtained using a Quartz Crystal Microbalance or a Differential Mobility Particle Sizer.

EXPECTED PRODUCTS/MILESTONES: This research will provide detailed information on pollutants produced in unvented tents from heaters that burn leaded diesel fuels. This information is needed to assess potential exposure of service personnel who served in the Persian Gulf War.

STATUS/RESULTS TO DATE: We are still unable to obtain (or purchase) the needed tent, heaters, and fuels used in the Persian Gulf from the Army. We are preparing the research protocol for the project. Currently the protocol is under the institutional approval process.

PUBLICATIONS none to date

Title Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War.

Research Focus: Reproductive Health Studies

Research Type: Epidemiology Research

Agency DoD

Study Location Sacramento, CA

Study Start Date 6/1/96

Estimated Completion Date 6/30/98

Project Status Ongoing

DoD-35

Summary

OVERALL PROJECT OBJECTIVE: To determine whether Reserve participants in the Persian Gulf War can be linked to vital statistics and Birth Defects Registry data.
SPECIFIC AIMS: 1) To determine if DoD computerized information is accurate compared to the hospital medical records and, 2) to determine the feasibility of investigating birth defects in the children of the Persian Gulf War veterans; and, 3) to answer the research questions.
STATUS/RESULTS TO DATE: Unable to begin due to delays by Army HSRRB to approve a necessary waiver.

PUBLICATIONS none to date

Title Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms

Research Focus: Brain & Nervous System

Research Type: Epidemiology/Clinical Research

Agency DoD

Study Location Dallas, TX

Study Start Date 6/15/96

Estimated Completion Date 7/14/98

Project Status Ongoing

DoD-36

Summary

OVERALL PROJECT OBJECTIVE: This research addresses the symptom of abnormal fatigue in Gulf War veterans. The study will examine the possibility that mechanisms used by muscle cells to use oxygen and produce energy for work may be impaired in patients suffering abnormal muscle fatigue and the inability to exercise.
SPECIFIC AIMS: On the basis of preliminary results of evaluation of symptoms of abnormal fatigability in Gulf War veterans, the researchers hypothesize that the common complaint of abnormal fatigue and exercise intolerance in these patients is attributable to impaired energy production via oxidative phosphorylation. Under this general hypothesis, the researcher will address four specific question: (1) Is there an abnormality in muscle oxygen utilization or oxygen transport to muscle during exercise in affected individuals? (2) Is there exaggerated metabolic muscle fatigue in exercise consistent with impaired energy production? (3) Is the metabolic and physiologic response to aerobic physical conditioning impaired in these patients? (4) Is there a specific pattern of impaired activities of mitochondrial oxidative enzymes or respiratory chain complexes to account for impaired oxidative metabolism on attenuated increases in oxidative capacity in response to physical training.
METHODOLOGY: To answer these questions the researchers will employ forearm and cycle exercise to determine maximal work and oxidative capacity and to compare fatigue and metabolic responses to similar workloads among patients and age- and weight-matched sedentary control subjects. The study will compare muscle metabolic and physiologic responses to aerobic training in patients and matched control subjects. The oxidative mechanism in blood will be monitored by measurements of blood levels of diffusible metabolites that reflect oxidative capacity; measurement of intramuscular metabolites using 31-phosphorus magnetic resonance spectroscopy; and by using infrared spectroscopy. A cohort of patients and control subjects will be used to evaluate the hypothesis that oxidative limitations detected with non-invasive testing is attributable to impaired function of the mitochondrial respiratory chain as assessed biochemically in biopsied muscle. Exercise protocols and non-invasive monitors of oxygen transport and utilization as well as detailed muscle biochemistry will be used to identify specific causes of exercise intolerance in patients.
EXPECTED PRODUCTS (MILESTONES):
STATUS/RESULTS TO DATE:

PUBLICATIONS none to date

Title Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats

Research Focus: Pyridostigmine Bromide **Research Type:** Basic Research

Agency DoD **Study Location** Gainesville, FL

Study Start Date 5/1/96 **Estimated Completion Date** 6/1/99

Project Status Ongoing DoD-37

Summary

OVERALL PROJECT OBJECTIVE: To determine effects of small doses, alone or in combination, in males and females. This multidisciplinary study using male and females rats will examine any neurobehavioral toxicity and immune response alterations after exposure to pyridostigmine bormide, permethrin and DEET alone and in combinations. Human lymphocyte cells will also be studied for inhibiton of immune response as a result of exposures to these materials.
SPECIFIC AIMS: The main hypothesis of this multidisciplinary study is that the administration of pyridostigmine bromide (PB), permethrin (PERM) and DEET as single agents, or in combination, results in neurobehavioral toxicity and an altered immune response. Furthermore, it is believed that females are significantly more sensitive to the effects of these agents than are males. To evaluate this hypothesis, experiments have been designed to measure various aspects of CNS functioning in the presence of sub-toxic doses of PB, PERM, and DEET in adult male and female rats. Doses for PB will be 3/10/30 mg/kg, for PERM will be 15/30/60 mg/kg and for DEET will be 50/200/500 mg/kg. In addition, plasma concentrations of PB, PERM, and DEET will be determined and their effects on cholinesterase activity will be correlated with CNS functioning. The neurobehavioral analyses will be complemented be an assessment of the immune response in the same subjects, as well in lymphocytes from health human volunteers.
The neurobehavioral test battery is designed to measure critical aspects of CNS functioning related to symptoms of generalized fatigue, gastro-intestinal disturbance, muscle and joint pain, headaches, and memory loss. The neurobehavioral test battery includes an assessment of spontaneous locomotor behavior and an analysis of overall CNS functioning, motivation and memory performance. This study extends observations from previous experiments in male rats exposed to toxic doses of pyridostigmine or permethrin to female rats and to the effects of PB, permethrin and/or DEET in combination. This study will also provide additional information on the motivational and memory aspects of CNS functioning.
METHODOLOGY: Chemical analyses will determine (1) the metabolism and elimination of PB, permethrin and DEET, alone and in combination, for male and female subjects who participated in the neurobehavioral experiments, and (2) how PB, permethrin and DEET, alone and in combination, affect cholinesterase activity in these same subjects. This information will allow the correlation of plasma concentrations of PB, permethrin and DEET with the behavioral observations.
EXPECTED PRODUCTS (MILESTONES): The immunological experiments will be conducted to determine the role of PB, permethrin and DEET and (1) Suppression of the first and second signal transduction pathways in T-lymphocytes, (2) Cytokine expression, and (3) B-lymphocyte function.
STATUS/RESULTS TO DATE: Project started 5/5/96; initial experiment just under way.

PUBLICATIONS none to date

Title Diagnostic Antigens of Leishmania tropica

Research Focus: Leishmaniasis
Research Type: Applied Research
Agency DoD
Study Location Seattle, WA
Study Start Date 6/1/96
Estimated Completion Date 5/31/98
Project Status Ongoing
DoD-38

Summary

OVERALL PROJECT OBJECTIVE: This research wil attempt to develop a sensitive method to detect infection with Leishmania tropica, or related species, in military personnel.
SPECIFIC AIMS: There are currently no defined antigens for use in the diagnosis of leishmaniasis. There is an urgent need for sensitive methods to detect infection with Leishmania tropica, or related species, in military personnel. The researchers have developed such tests for other Leishmania species, and have isolated and characterized L. tropica antigens reactive with sera from L. tropica infected Gulf War veterans.
This study will attempt to develop similar tests for L. tropica using these recombinant L. tropica antigens. Effort will also be directed at cloning additional L. tropica antigens reactive with L. tropica infection sera and antigens that stimulate T-cells from individuals with L. tropica infection.
METHODOLOGY: Emphasis will be given to expressed genes which are highly sensitive. Inserts will be sequenced for determination of epitopes which may be produced synthetically. Recombinant or synthetic peptides will be evaluated by ELISA for their ability to detect antibody in patient sera. In related studies, cloned gene products will be evaluated for their ability to elicit patient T-cell response in vitro. These evaluations will include proliferation and cytokine production. Emphasis will be placed on finding antigens which are shared between Leishmania species having the ability to elicit strong T-cell responses. Such antigens will be candidates for skin test antigens and vaccine production.
EXPECTED PRODUCTS (MILESTONES):
STATUS/RESULTS TO DATE: Several new peptides of Lt-1 antigen have been made and evaluated them as serological reagents. Also, screening of L.tropica genomic libraries for new antigens have begun.
PUBLICATIONS none to date

Title A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency DoD

Study Location London, England

Study Start Date 6/1/96

Estimated Completion Date 6/30/99

Project Status Ongoing

DoD-39

Summary

OVERALL PROJECT OBJECTIVE: This research addresses the prevalence of unexplained illnesses, including chronic fatigue-like symptoms, in members of the United Kingdom Armed Forces who were deployed to the Persian Gulf during the Gulf War and who have served, and are serving in Bosnia.
SPECIFIC AIMS: This study is a two stage cohort study. Stage 1 consists of a postal health screening questionnaire to be sent to three groups who were/are in the Armed Forces; those who served in the Persian Gulf, those who served in Bosnia, and those who served in neither the Persian Gulf or Bosnia. The second stage involves performing neurophsychological tests on cases identified by stage 1 and a control group.
METHODOLOGY: This epidemiological study of the prevalence of unexplained illnesses in the populations at risk will use a two-stage design. Stage 1 will be a questionnaire survey of 3000 Gulf War veterans selected at random, an equivalent sample of Bosnia veterans, and appropriate control groups for each. Stage II will involve interview, examination, and testing of all those (approximately 10%) in Stage I who fall above a cutoff defining subjective health. Information gathered at Stage II will be used to estimate the prevalence of diagnosed and unexplained morbidity, including chronic fatigue symptoms, in UK service personnel, and to calculate whether there is an excess associated with Gulf War and/or Bosnia service. If there is, then the researchers will be able to examine pre-morbid and psychosocial factors which may be implicated in such an increase, as well as identify avenues for further biological and psychosocial research.
This epidemiological study should ascertain if service in the Gulf War by UK armed forces personnel was associated with an increase in physical and/or psychological morbidity, and if so, if there is evidence of an increase in either new or ill-defined conditions such as chronic fatigue syndrome, or an illness peculiar to Gulf War service.
EXPECTED PRODUCTS (MILESTONES): Reports and publications.
STATUS/RESULTS TO DATE: Project at the questionnaire design stage.

PUBLICATIONS none to date

Title Psychological and Neurobiological Consequences of the Gulf War Experience

Research Focus: Brain & Nervous System

Research Type: Epidemiology/Clinical Research

Agency DoD

Study Location VAMC West Haven, CT

Study Start Date 6/7/96

Estimated Completion Date 7/6/99

Project Status Ongoing

DoD-40

Summary

OVERALL PROJECT OBJECTIVE: To determine the nature of memory for traumatic events as they relate to PTSD symptomatology.
SPECIFIC AIMS: To examine the course of memory for traumatic events over time and the brain areas believed to be altered due to trauma.
METHODOLOGY: Longitudinal follow-up of a cohort of veterans of Operation Desert Storm (e.g. questionnaires, ratings scales). MRI study of 30 Desert Storm veterans with PTSD. This research will continue to follow the course of symptoms of Post-Traumatic Stress Disorder in a population of Gulf War veteans. This study of how such symptoms, as well as memory function, change over time in the veterans will lead to a better understanding of PTSD and the elements of risk that would cause and continue PTSD symptoms over time.
The study is in two parts. The first part is a longitudinal descriptive study of trauma-related symptomatology in Gulf War veterans. The second part is an investigation of memory function and hippocampal volume in Gulf War veterans who meet criteria for pos-traumatic stress disorder (PTSD). Results of the researchers' previous work with a cohort of Gulf War veterans indicated that there was an overall increase in PTSD symptomatology in the veterans over the first two years following the Gulf War. With regard to memory testing, there were many instances of inconsistent recall for events that were objective and highly traumatic in nature. The data do not support the position that traumatic memories are fixed or indelible and suggest that as PTSD symptomatology increases, so does amplification of memory for traumatic events.
This study continues the original methodology for the fifth, sixth and seventh post-war years. It is anticipated that a high percentage of subjects who have already participated in this research can be recruited to continue in this project and that at least 100 new subjects can also be recruited. It is anticipated that a better understanding of the longitudinal course of trauma-related symptomatology and risk factors for the development and maintenance of these symptoms would have implications for treatment.
The second part of the study will examine the possibility that memory deficits in the subject population are relatively broad-based and reflect problems at several levels of information processing, including acquisition, retention and/or retrieval and that these memory deficits may be related to decreased hippocampal volume. Results of this study would make it possible to determine whether these abnormalities are present in a variety of combat populations and whether such abnormalities can be detected at earlier stages than in the previously-studied Vietnam veteran population. Potential relationship to clinical symptomatology and psychosocial functioning will also be investigated.
EXPECTED PRODUCTS/MILESTONES: We expect to show that memory for traumatic events is not consistent over time, and that there may be associated decrease in hippocampal volume in PTSD.
STATUS/RESULTS TO DATE:

PUBLICATIONS none to date

Title Evaluation of Muscle Function in Persian Gulf Veterans

Research Focus: Brain & Nervous System

Research Type: Epidemiology/Clinical Research

Agency DoD

Study Location Philadelphia, PA

Study Start Date 6/15/96

Estimated Completion Date 11/14/99

Project Status Ongoing

DoD-41

Summary

OVERALL PROJECT OBJECTIVE: The major objective of this research is to investigate the etiology response for the ongoing chronic fatigue and muscle weakness in Gulf War veterans with unexplained illnesses by evaluating abnormalities in skeletal muscle function in Gulf War veterans.
SPECIFIC AIMS: 1. To evaluate skeletal muscle in Persian Gulf veterans with severe chronic fatigue and persian Gulf veterans with no medical complaints (healthy controls); 2. To determine the relationship between the severity of chronic fatigue in Persian Gulf veterans and the degree of muscle dysfunction; 3. To compare muscle function in Persian Gulf veterans with severe chronic fatigue with muscle function in healthy sedentary civilians and civilians with chronic fatigue.
METHODOLOGY: The goal of this proposal is to evaluate skeletal muscle in Persian Gulf veterans. Our major hypothesis is that Persian Gulf veterans who present a symptom profile consistent with chronic fatigue suffer from muscle dysfunctioning. In addition, we hypothesize that the severity of chronic fatigue in this population is related to the degree of muscle dysfunctioning. To test these hypotheses, a battery of tests will be performed on Persian Gulf veterans with severe chronic fatigue (n=50) and on Persian Gulf veterans who were deployed but who have no medical problems (n=50). The evaluation will consist of the following measurements: 1. Functional assessment as reflected in isometric and isokinetic measures; 2. In vivo metabolic measures as determined by 31P-Magnetic Resonance spectroscopy (MRS); 3. In vivo morphological measures as determined via Magnetic Resonance Imaging (MRI); 4. Histological analyses of muscle biopsies; 5. Electromyographic evaluation of motor unit recruitment; 6. Muscle enzyme levels; 7. Genetic screening.
EXPECTED PROJECTS (MILESTONES): This project runs over three years. The first 6 months serve to recruit the subjects and to train the necessary personnel. The following two years will be used to collect all the data at a rate of approximately 1 subject/week. So that at the end of the first year we will have tested 13 Persian Gulf veterans with chronic fatigue and 13 healthy veterans. At the end of the second year. we should have tested another 24 subjects with chronic fatigue and 24 healthy controls. For the first 6 months of the third year we will test the final 13 veterans with chronic fatigue and 13 controls, so that the data collection will be completed at the end of 2.5 years. The final 6 months of this 3 year period will be used to analyze and interpret the data, to disseminate the results to the Department of Defense and the veteran community, and to write scientific papers.
STATUS/RESULTS TO DATE: Recruiting of subjects has been started, necessary personnel is being trained.

PUBLICATIONS none to date

Title The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment

Research Focus: Symptoms/General Health

Research Type: Epidemiology/Clinical Research

Agency DoD

Study Location VAMC Birmingham

Study Start Date

Estimated Completion Date

Project Status Pending Funding

DoD-42

Summary

OVERALL PROJECT OBJECTIVE: Soon after the resolution of the Persian Gulf War, veterans were seen with a variety of complaints alleged to be related to the conflict. Many of the complaints were vague and relatively non-specific (i.e. myalgias, arthralgias, headaches or memory loss). However, in association with intense media publicity, the term Persian Gulf War syndrome was coined. Attempts to define a specific clinical spectrum seen in this 'disorder' have not been successful. Nonetheless, a number of potential causes have been discussed and include exposures to organophosphates, pyridostigmine, petrochemical combustion products, depleted uranium from projectiles and exposure to a variety of endemic infectious agents including leishmania and mycoplasma. There are a few isolated reports of identification in the urine of organisms from symptomatic veterans and treatment successes with long term antibiotics or demonstration of genetic material from mycoplasma in blood of symptomatic veterans. It is not clear from these reports that such studies have been adequately controlled, nor have they been replicated.

Additionally, based on complaints such as fatigue and memory loss, it has been speculated that there may be neuropsychiatric abnormalities responsible for many of the complaints seen in veterans returning from the Persian Gulf war.

However, at this time, there is little compelling evidence that any of these are major factors in the majority of symptomatic Persian Gulf veterans. At this point it is not even clear that veterans from the Gulf War have different symptoms than patients from other conflicts or for that matter, civilians without military service.

The Birmingham VAMC has been very active in evaluating patients returning from the Persian Gulf war. Approximately 1400 individuals have been seen and have had evaluations. Of these, about 10-15% are asymptomatic. Of the remaining 85%, approximately 90% have a diagnosable illness. Clearly, it is important to define the spectrum of their illnesses and determine factors which may be contributing to the development of their symptoms. Additionally, a number of Persian Gulf veterans, which we estimate conservatively as 100 of those seen at the BVAMC, are symptomatic and do not have defined illnesses. An adequately controlled study investigating veterans who have an undiagnosed illness to determine if there are fundamental neuropsychiatric or immunlogic abnormalities would be important in either validating claims or allaying fears regarding postulates of abnormalities in these areas. To answer these questions, we propose a case control format.

SPECIFIC AIMS: The specific goals of this proposal are to:

1) evaluate self-reported conditions in Persian Gulf veterans to determine if they represent described and accepted medical conditions and/or are associated with objective findings which would validate these symptoms.

2) evaluate symptomatic Gulf war veterans to determine risk factors which may identify veterans who have reported symptoms.

3) evaluate in a controlled fashion symptomatic, but undiagnosed, Persian Gulf war veterans to determine if there is a definable immunologic or neuro-psychiatric abnormality.

METHODOLOGY: This study will determine whether specific immunological or neuropsychiatric abnormalities can be detected in GW participants who are symptomatic, but in whom no specific diagnosis has as yet been made. These studies may uncover an immunological basis for some of the broad types of symptoms reported by GW veterans. This proposal attempts to get at the heart of the problem cited in the Institute of Medicine (IOM) report, that GW veterans' mystery illnesses

may not be a single illness and that it is important to study various possible causes and the interactions between causes. This work will build upon previous work and local programs. The use of advanced methodology in the imaging, immune, mycoplasma and oxicant injury study is important. Sample sizes are adequate and support for statistical analysis is an integral part of the proposal.
EXPECTED PRODUCTS (MILESTONES): Reports and publications.
STATUS/RESULTS TO DATE: This study has not been awarded yet, therefore, there is no start or estimated completion dates.

PUBLICATIONS none to date

Title Investigation of Seminal Plasma Hypersensitivity Reactions

Research Focus: Reproductive Health Studies

Research Type: Epidemiology/Clinical Research

Agency DoD

Study Location Univ. Cincinnati MSC

Study Start Date 11/1/96

Estimated Completion Date 10/1/99

Project Status Pending Funding

DoD-44

Summary

OVERALL PROJECT OBJECTIVE: This study is a coordinated effort to determine whether the Gulf War vaginal burning syndrome is due to immune responses previously described for women in the general community diagnosed with seminal plasma hypersensitivity.
SPECIFIC AIMS: Military and veteran sources will be surveyed to obtain a population of women who developed vaginal burning syndrome after their sexual partners returned from the Persian Gulf.
METHODOLOGY: The population of women with Gulf War vaginal burning syndrome will be compared to our civilian population with seminal plasma hypersensitivity. Relevant seminal plasma proteins will be characterized using immunoaffinity column chromatography, isoelectric focusing, immunoelectrophoresis and SDS-PAGE using seminal plasma from the male sexual partners of experimental and control female groups. Once characterized these proteins will be used for determination of specific immune responses in all groups. Seminal plasma proteins from normal males with and without Gulf War exposure will be exposed to a number of different in vitro chemical conditions (i.e. pyridostigmine, pesticides), vaccines and extreme heat. These proteins will be characterized before and after exposure using functional assays whichmeasure antibody response, complement activation and cellular proliferation. Relevant seminal plasma proteins will undergo amino acid sequencing to determine whether homology with other proteins exist. the effect of an immunosuppressive protein (fraction 1) in humal seminal plasma will also be investigated before and after in vitro exposure to a variety of physical and chemical factors encountered during the gulf war.
EXPECTED PRODUCTS (MILESTONES): If the hypotheses are correct, 1) women with seminal plasma hypersensitivity and vaginal burning syndrome will demonstrate immediate cutaneous rectivity to seminal plasma protein fractions; 2) one or more semical plasma proteins that cause localized vaginal symptoms in our civilian group of women will also cause similar symptoms in women with Gulf War vaginal burning syndrome; and 3) the ability of seminal plasma proteins to regulate (either stimulate or inhibit) the humoral, cellular or secretory immune responses after exposure to physical and chemical factors encountered in the Gulf War.
STATUS: Study just started (11/96 award)

PUBLICATIONS none to date

Title Physical and Emotional Health of Gulf War Veterans Women

Research Focus: Symptoms/General Health

Research Type: Epidemiology/Clinical Research

Agency DoD

Study Location Ann Arbor, MI

Study Start Date 9/1/96

Estimated Completion Date 8/31/99

Project Status Ongoing

DoD-45

Summary

OVERALL PROJECT OBJECTIVE: This study will compare the prevalence of general and gender specific health problems in 900 Air force women deployed to the gulf and 900 Air force women deployed elsewhere.
SPECIFIC AIMS: To assess whether the prevalence of health problems remain elevated in women deployed to the Gulf at six years post deployment, after controlling for potentially confounding factors such as age, reproductive history, sexual history and lifestyle factors.
METHODOLOGY: This research is to describe the incidence, prevalence, and nature of symptoms associated with Persian Gulf War service within a randomized sample of Air Force women. Our design is developed on previous experience with two studies of Gulf War veteran women as well as the recommendations of numerous military and civilian scientific groups established to address this body of research. Specifically, in previous studies we have used a comparison group of women deployed to sites other than the theater of the war under the assumption they were physiclly fit for duty and would provide a better comparison than those who did not deploy perhaps for physical health reasons. Futher sampling strategies will follow the recommendations for both the National Institutes of Health (NIH, 1994) and the Institute of Medicine (IOM, 1995; Roberts, 1995), who both call for well-designed epidemiologic studies. In both our previous studies we used a randomized stratified factorial design (theater vs. non-theater; parent vs. non-parent; and component (active, guard, and reserve). Similar sampling procedures will be used in this study in order to control for potentially confounding effects of component and patrental status. This study will also include detailed information on sexual, reproductive, and menstrual history to allow for more completeanalyses of findings.
Sample size and power will detect differences ovserved in previous studies. Data collection involves recruiting the study participants and maximizing the response rate while minimizing attrition. A single comprehensive questionaire will provide basic demographic, socionomic, and background information and include measures of general physical health and measures of gender-specific health. Mental health measures include assessment of depression, somatization, and 8 PTSD specific to Gulf War service and will include a stressful life event measure. Data processing includes all appropriate range and logic checks. Stastical analyses include descriptive stastics, cross tabulations with chi-square and t-tests, distrbutions, and multiple regression analyses for health outcomes and deployment status.
EXPECTED PRODUCTS (MILESTONES): Three project years: 1) all planning and pretesting during year 1; one-half of data collection (mail administrtion) in year 1 and the second half in year 2; all coding and data entry in year 2; and the final report and electronic data file as deliverables.
STATUS: Study has just started year 1 tasks.

PUBLICATIONS none to date

Title Exploratory Data Analysis with the CCEP Database

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency DoD

Study Location Naval Post-Graduate School, Mo

Study Start Date 10/1/95

Estimated Completion Date 9/1/97

Project Status Ongoing

DoD-46

Summary

OVERALL PROJECT OBJECTIVE: To systematically examine the database for interesting relationships, and to find, with a high level of confidence, the most interesting ones without having to do an exhaustive search.
SPECIFIC AIMS: 1) to develop a generic computer package to do exploratory data analysis using genetic algorithms to decide which attributes to consider in the analysis; 2) to apply this package on a number of specific application runs relevant to the Gulf War Syndrome problem; 3) to produce, analyze, and comprehensively document the results of these runs, and produce a set of findings and conclusions.
METHODOLOGY: For the search problem over the space of attributes found in the CCEP database, the main search methodology is based on genetic algorithms. The overall solution methodology consists of exploratory data analysis and knowledge discovery in databases.
EXPECTED PRODUCTS (MILESTONES): 1. The computer software: a) a hypothesis generator module; b) a filtering module; and c) a results presentation and interpretation module.
STATIS/RESULTS TO DATE:Version 1.0 of the Hypothesis Generator Module is complete, tested, and applied in a series of production runs.

PUBLICATIONS none to date

Title Study of Mycoplasmal Infections in Gulf War Veterans

Research Focus: Miscellaneous
Research Type: Epidemiology/Clinical Research
Agency DoD
Study Location Walter Reed Army MC
Study Start Date 10/10/95
Estimated Completion Date 8/30/97
Project Status Ongoing
DoD-47

Summary

OVERALL PROJECT OBJECTIVE: This study is designed to find evidence for mycoplasmal infections in symptomatic Operation Desert Storm veterans, by comparing the rate of seroconversion in symptomatic veterans as compared to healthy Gulf veterans and by culturing for Mycoplasma organisms in symptomatic and healthy Gulf veterans.
SPECIFIC AIMS: See objectives.
METHODOLOGY: This study has two parts: (1) Sera from 200 symptomatic Gulf veterans and 200 healthy Gulf veterans, stored in the U.S. Armed Forces HIV Repository are used. Sera prior to and after deployment to South West Asia are tested for antibody to M. fermentans, M. genitalium, and M. penetrans. (2) Blood, urine, oropharyngeal, and rectal samples in 100 consecutive veterans undergoing evaluation at WRAMC and 100 asymptomatic veterans are tested for evidence of mycoplasmal infection by culture, serology and PCR.
EXPECTED PRODUCTS (MILESTONES): August 1996 - Initial Part One results; March 1997 - Addendum Part One results; August 1997 - Part Two complete.
STATUS/RESULTS TO DATE: Part one of the study was done using 151 cases and 151 age and gender matched controls. There was no statistically significant difference in the seroconversion rate to any of the aforementioned Mycoplasma. However the seroconversion rate was unexpectedly low: 1.5% for controls and 3.0% in cases for M. fermentans. The odds ratio (OR) for cases compared to controls was 2.0 with a confidence interval of 0.4 - 10.9. In order to be able to detect an OR of 2 with a background seroconversion rate of 1 - 2% with 80% power, a larger study needs to be done. An addendum to the protocol has been submitted. Part two of the study is still ongoing, and as of 9 Sep 1996, 41 symptomatic veterans and 18 healthy controls have entered the study.
No significant difference in the seroconversion rate to Mycoplasma has been found when comparing symptomatic to healthy Gulf veterans. Because of the low seroconversion rate, the power of part one of the study is low and a larger sample size will allow a better estimation of seroconversion to Mycoplasma in this population.

PUBLICATIONS none to date

Title Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf-War Syndrome Cohort vs Selected Control Groups

Research Focus: Immunology
Research Type: Epidemiology/Clinical Research
Agency DoD
Study Location Ft. Detrick
Study Start Date 10/10/95
Estimated Completion Date 5/31/97
Project Status Ongoing
DoD-48

Summary

OVERALL PROJECT OBJECTIVE: This study is designed to determine the frequency of chromosome 7 inversions in blood lymphocytes of four groups of volunteers: (1) symptomatic Gulf War veterans with findings consistent with a diagnosis of autoimmune or collagen vascular disease; (2) Gulf War veterans without abnormalities; (3) symptomatic volunteers with autoimmune or collagen vascular disease; and (4) healthy volunteers with no Gulf War exposure.
SPECIFIC AIMS: See objectives.
METHODOLOGY: Blood will be obtained from twenty five consecutive cases of each of the four groups. The samples are examined for the chromosome 7 inversion blindly in the laboratory of Dr. William Fishbein, an investigator from the AFIP. After the 100 samples the investigators will be unblinded and a statistical analysis will be done.
EXPECTED PRODUCTS (MILESTONES): March 1997 - Collection complete; April 1997 - Analysis complete.
STATUS/RESULTS TO DATE: As of 9 September 1996, a total of 75 volunteers have been enrolled in the study.
No conclusions can be drawn at this time because the groups remains blinded to investigators.

PUBLICATIONS none to date

Title Health Assessment of Persian Gulf War Veterans from Iowa

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency HHS

Study Location CDC and Prevention, Iowa

Study Start Date 12/1/94

Estimated Completion Date 1/31/98

Project Status Ongoing

HHS-1

Summary

OVERALL PROJECT OBJECTIVE: The objective of this study is to assess the prevalence of adverse health outcomes among a random sample of Persian Gulf War veterans who listed Iowa as their home of record. For comparison purposes, this study will also assess the prevalence of adverse health outcomes among a control sample of military personnel who served during the time of the Persian Gulf War, but who were not deployed to the Persian Gulf theater of operations.
SPECIFIC AIMS: This study will address the following specific hypotheses: (1) Persian Gulf War veterans experienced more self-reported health problems in the post-war period than did Persian Gulf-era military personnel who did not serve in the Persian Gulf region; (2) active duty military personnel with service in the Persian Gulf region experienced more self-reported health problems in the post war period than did active duty military personnel who did not serve in the Persian Gulf region; (3) National Guard and reserve personnel with service in the Persian Gulf region experienced more self-reported health problems in the post-war period than did National Guard and reserve personnel who did not serve in the Persian Gulf region; and (4) National Guard and reserve personnel with service in the Persian Gulf region experienced more self-reported health problems than active duty military personnel with comparable service.
METHODOLOGY: Data on self-reported health outcomes are being collected through a telephone survey with a random sample of Persian Gulf War veterans and Persian Gulf War-era controls who listed Iowa as their home of record. Approximately equal sample sizes from four groups of military personnel were selected: (1) exposed (served in Persian Gulf) active duty military personnel; (2) exposed National Guard and reserve personnel; (3) control (Persian Gulf War-era) active duty military personnel; and (4) control National Guard and reserve personnel. Approximately 750 subjects in each group will be interviewed using stratified random sampling with proportional allocation. In addition, each group will be stratified based on branch of military service, pay grade, race, age, and gender.
EXPECTED PRODUCTS (MILESTONES): Expect report of results by early 1997.
STATUS/RESULTS TO DATE: Ongoing; Data collection completed May 1996, initial report submitted for publication in September 1996.

PUBLICATIONS none to date

Title Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency HHS

Study Location CDC, Pennsylvania

Study Start Date 12/1/94

Estimated Completion Date 3/31/95

Project Status Ongoing

HHS-2

Summary

OVERALL PROJECT OBJECTIVE: Evaluate reported cluster of illness in the Pennsylvania 193rd Air National Guard unit.
SPECIFIC AIMS: To characterize patients, determine if there was a cluster, and to identify risk factors for cluster.
METHODOLOGY: Case series survey, cross sectional population survey, and case control study
STATUS/RESULTS TO DATE: EPI - AID is complete. Lab and data analysis continue.

PUBLICATIONS Morbidity and Mortality Weekly Report: Unexplained Illness Among Persian Gulf War Veterans in an Air National Guard Unit, Preliminary Report, August 1990-March 1995. MMWR, 44(23):443-447, 1995.

Title Biomarkers of Susceptibility and Polycyclic Aromatic Hydrocarbon (PAH) Exposure in Urine and blood Cell DNA from U.S. Army Soldiers Exposed to Kuwaiti Oil Well Fires

Research Focus: Environmental Toxicology

Research Type: Basic Research

Agency HHS

Study Location NIH/NCI/DCE/LCTP/IVP

Study Start Date 1/1/92

Estimated Completion Date 1/31/97

Project Status Ongoing

HHS-3

Summary

OVERALL PROJECT OBJECTIVE: To compare PAH level in soil and air with biomarkers of exposure (urinary metabolites), biologically-effective dose (DNA adducts) and individual susceptibility (genetic polymorphisms) for this group of 62 soldiers. This project is technically not a research project. It was an analysis requested by the U.S. Army Environmental Hygiene Agency, now known as the Center for Health Promotion and Preventive Medicine, as a part of their ongoing exposure assessments.

SPECIFIC AIMS: To determine the extent of exposure and the correlation between these various biomarkers.

METHODLOGY: Solidiers participating in a USAEHA surveillance project in which ambient PAH monitoring and biomonitoring were performed. Samples of blood and urine were taken in Germany in June (1991), in August, eight weeks after deployment to Kuwait, and in October after the return to Germany. PAH-DNA adducts were measured by benzo[a]pyrene-DNA dissociation-enhanced lanthanide fluroimmunoassay (DELFIA) and aromatic DNA adducts were measured by 32P-postlabeling in blood cell DNA. Urinary benzo[a]pyrene metabolites are being determined by immunaffinity chromatography and fluorescence. Glutathione-s-transferase and cytochrome P450 1A1 polymorphisms have been determined by PCR amplification of the DNA.

EXPECTED PRODUCTS (MILESTONES): The anticipated findings were higher pollution in the area of the soldiers' duty stations and higher levels of DNA adducts and urinary metabolites.

STATUS/RESULTS TO DATE: By both methodologies, blood cell DNA adduct measurements were lower in Kuwait than in Germany in June and October. The increase in adduct levels in October (compared to August in Kuwait) was statistically significant. Urinary metabolite studies are not complete. The data suggest that the location of the soldiers' duty stations in Kuwait represented a cleaner working environment than Germany. Actual PAH measurements of air and soil in Kuwait showed very low levels of contamination. Literature values for ambient PAH measurements for Germany at the same time are much higher.

PUBLICATIONS none to date

Title Suspected Increase of Birth Defects and health Problems Among Children Born to Persian Gulf War Veterans In Mississippi

Research Focus: Reproductive Health
Research Type: Epidemiology Research
Agency CDC
Study Location Jackson
Study Start Date 5/1/94
Estimated Completion Date 2/1/96
Project Status Complete
HHS-4

Summary

OVERALL PROJECT OBJECTIVE: To determine the nature and extent of a reported increase of birth defects and health problems among children born to Persian Gulf War veterans from two units of the Mississippi National Guard.
SPECIFIC AIMS: To calculate the number and rate of birth defects and health problems in children born to Persian Gulf War veterans from two units of the MS National Guard after their return from overseas service, and determine whether an excess of birth defects/health problems occurred.
METHODOLOGY: Descriptive survey by medical record review, supplemented by parent/physician interview as required. Comparison of observed numbers/rates with expected numbers/rates from birth defect surveillance systems, epidemiological studies, etc.
EXPECTED PRODUCTS (MILESTONES): Final report published by CDC on 12/19/94 (Field Epidemiology Report #95-01).
STATUS/RESULTS TO DATE: The total number of all types of birth defects was not greater than expected. The frequency of premature birth, low birth weight, and other health problems appeared similar to that in the general populaton.

PUBLICATIONS
Penman AD, Tarver RS. No evidence of increase in birth defects and health problems among children born to Persian Gulf War veterans in Mississippi. Military Medicine, 161(1):1-5, 1996.

Title Mortality Follow-up Study of Persian Gulf Veterans

Research Focus: Mortality
Research Type: Epidemiology Research
Agency VA
Study Location VACO
Study Start Date 7/1/94
Estimated Completion Date 7/1/3196
Project Status Complete
VA-1

Summary

OVERALL PROJECT OBJECTIVE: VA's Environmental Epidemiology Service is undertaking a retrospective Follow-up Mortality Study of Persian Gulf Veterans that will compare the overall mortality rates and cause-specific mortality rate of all 697,000 servicemembers who served in the Persian Gulf theater of operations anytime between August 1990 and May 1991 with those of a comparison group of 803,526 service members randomly selected from various subsets of all servicemembers who were in service anytime between August 1990 and May 1991 but who were not deployed to the Persian Gulf theater.
SPECIFIC AIMS: Are there excess deaths among Persian Gulf veterans from various natural and external causes in comparison to their non-Persian Gulf Veteran counterparts?
METHODOLOGY: A retrospective cohort mortality study; 697,000 study subjects, 800,000 controls; Cox regression model, SMR analysis. Vital status has been determined using a VA database known as the Beneficiary Identification and Record Locator Subsystem (BIRLS) and a Social Security Administration file for deaths reported through 1993. Death certificates have been requested from VA regional offices, Federal Records Centers or from state vital statistics offices. Cause of death are coded by a qualified nosologist using the International Classification of Diseases, 9th revision, without the knowledge of whether the decedent served in the Persian Gulf area.
As the first mortality follow-up of Persian Gulf veterans, this study represents an important first step in addressing the health concerns of Persian Gulf veterans. The study results as reflected in mortality should provide an early warning for any possible life threatening health conditions as a consequency of Persian Gulf service. The study will be periodically updated to ascertain any long-term consequences of Persian Gulf service on mortality outcomes.
EXPECTED PROEJCTS (MILESTONES): Data collection is complete. Preliminary results were presented at the American Public Health Association Meeting in San Diego CA October, 1995. A final report was submitted in April 1996 to a scientific journal for publication.
STATUS/RESULTS TO DATE: Preliminary analysis indicates that the overall mortality rate is higher in Persian Gulf veterans compared to non-deployed era veterans. However, when causes due to accident, suicide and homicide are accounted for, there is no difference in mortality rate between the two groups.

PUBLICATIONS Manuscript accepted for publication.

Title National Health Survey of Persian Gulf Veterans

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency VA

Study Location VACO

Study Start Date 7/1/94

Estimated Completion Date 6/30/98

Project Status Ongoing

VA-2

Summary

OVERALL PROJECT OBJECTIVE: To estimate prevalence of various symptoms and other health outcomes for Persian Gulf War veterans.
SPECIFIC AIMS: To estimate and compare prevalence of various symptoms, medical conditions, and unexplained illnesses in Persian Gulf war veterans and those of non-Persian Gulf veterans.
METHODOLOGY: A population-based health survey. Several studies are currently underway that investigate the incidence, prevalence, and nature of illnesses in Gulf War veterans. The National Health Survey of Persian Gulf Veterans and Their Family Members is conducted in three phases. In Phase I, a questionnaire was mailed to each of 30,000 veterans (15,000 Persian Gulf Veterans; 15,000 non-Persian Gulf Veterans). Multiple follow-up mailings were made to increase the response rate. In Phase II, a sample of 8,000 non-respondents will be randomly selected and a telephone interview will be attempted using a CATI questionnaire which includes a question on reasons for refusal. Telephone interviews with the non-respondents will assist in assessing potential non-respondent bias and will supplement the postal survey data. In addition, during Phase II, selected self-reported data collected by the postal questionnaire will be validated through records review for 2,000 veterans from each group. In Phase III, the same 2,000 veteran respondents and their family members from each group will be invited to participate in a comprehensive physical examination under a uniform comprehensive clinical examination protocol at a VA, DoD, or private medical facility.
The scope of the survey spans 3 years: Phase I was completed at the end of the first year (June 1996); Phase II by October 1997; and Phase III by the end of the third year (June 1998).
EXPECTED PROJECTS (MILESTONES): Publication in a peer-reviewed journal.
STATUS/RESULTS TO DATE: The proposed study protocol and questionnaire were peer-reviewed and approved by an external scientific oversight committee in April 1995. The proposed survey questionnaire was approved by the Office of Management and Budget (OMB) in September 1995. The initial questionnaires were mailed in November 1995 and the first supplemental questionnaires were mailed in January 1996 to 20,426 non-respondents and individuals with new mailing addresses. Phase I of the survey was completed in June 1996.

PUBLICATIONS none to date

Title Use of Roster of Veterans Who Served in Persian Gulf Area

Research Focus: Miscellaneous
Research Type: Epidemiology Research
Agency VA/DoD
Study Location VACO
Study Start Date 7/1/94
Estimated Completion Date 7/31/96
Project Status Ongoing
VA-3

Summary

OVERALL PROJECT OBJECTIVE: To properly address the issue of possible exposure to environmental hazards, all individuals who served in the Persian Gulf region need to be identified.
SPECIFIC AIMS: To prepare a computer file of over 697,000 troops assigned to the Persian Gulf area during Operation Desert Shield/Desert Storm.
METHODOLOGY: The U.S. Army and Joint Services Environmental Support Group (ESG) is in the process of computerizing troop unit locations in the Persian Gulf Theater.
EXPECTED OUTCOMES (MILESTONES): Complete description of unit locations in the Persian Gulf Theater.
STATUS/RESULTS TO DATE: The personnel database is now operational (about 700,000 individuals). Troop movement software is now operational. Documenting troop movements from Combat Records is continuing and is over 90% complete, based on the records currently identified. This database has been made available to VA's Environmental Epidemiology Service (EES), giving VA access to demographic data on all troops stationed in the Persian Gulf. The risk assessment data are obtained, and oil field emissions modeling data are synthesized. Initial results of unit-level values are expected in May of 1996.
RESULTS: Troop roster and troop unit locations were available as of the end of July 1996.

PUBLICATIONS none to date

Title Evaluation of Cognitive Functioning of Persian Gulf Veterans

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC Boston

Study Start Date 10/1/94

Estimated Completion Date 9/30/99

Project Status Ongoing

VA-4A

Summary

OVERALL PROJECT OBJECTIVE: The primary focus of this research project is to determine whether specific cognitive deficits or deficit patterns are associated with the presence of self-reported health complaints and/or with hazardous environmental exposures in the Gulf. (Exposure information will be obtained either from self-report, exposure modeling, and DoD data on troop locations). In examining these associations, the influence of war-zone stress, PTSD symptomatology, psychological distress, and post-deployment life stressors is being evaluated.
SPECIFIC AIMS: The specific objectives of this study are: (1) to observe and determine whether cognitive performance deficits are associated with self-reported health complaints stemming from Persian Gulf deployment; (2) to determine the relationship of environmental exposure (self-report and based on an independent exposure protocol) during deployment to cognitive performance; (3) to characterize subsets of cognitive patterns or deficits among exposure classes; (4) to delineate the association of cognitive alterations or deficits with levels of combat exposure, combat stress, and PTSD symptomatology; and (5) to conduct a preliminary examination of the relationship among health symptoms, hazardous environmental exposure, and other war-zone experiences, specifically traumatic war-time stressors and ensuing trauma symptomatology (Sutker, Uddo, Brailey, & Allain,1993; Wolfe, Keane, & Young, in press). Identification of diagnostic predictors and their relationship to outcomes of interest will help establish preliminary models related to important components of the military experience. The development of these models will aid Department of Veterans Affairs (VA) and Department of Defense (DoD) activities related to veterans' health care by: (1) facilitating symptom recognition and diagnosis in areas of growing concern (environmental exposure and traumatic stress following war), (2) emphasizing interdisciplinary approaches, (3) contributing to treatment planning, and (4) providing a baseline against which cognitive and mental status change over time can be gauged. Observations and findings from this study can lead to more focused investigation of cognitive functions that may be directly associated with defined exposures and/or PTSD symptomatology.
METHODOLOGY: Subjects in this face-to-face study are contacted by phone and asked to participate in as many parts of the protocol as they would like. The protocol consists of an in-depth questionnaire which asks about background information relating to job, education, family history, medical and psychological problems, an interview with an Environmental Health specialist about experiences and exposures while in the Gulf, a psychological interview with a clinical psychologist asking about readjustment issues and psychiatric stress since the war, and neuropsychological tests examining primarily memory, attention, and learning abilities.
EXPECTED PRODUCTS (MILESTONES): Multiple scientific manuscripts, annual reports, annual reports of Boston Environmental Hazards Center, longitudinal data on stress and health.
STATUS/RESULTS TO DATE: This study constitutes Time 3 of the Desert Storm Reunion Survey. The Ft. Devens ODS Reunion Survey represents a longitudinal assessment of readjustment of Persian Gulf War veterans returning through Ft. Devens, Massachusetts, following their return from the Persian Gulf region.
To date, 220 subjects from the Devens cohort sample have been tested (137 have come to the Boston VAMC and completed all parts of the protocol; 83 have partially completed the protocol generally because they live geographically too far away). In addtion, 47 veteran subjects (part of the larger Devens cohort but not the projected sample), and 50 controls (veterans deployed to Germany but not the Gulf) have completed the Project #1 protocol).

In order to substantiate and corroborate information reported to us by veterans regarding where they were located and potential hazardous exposures in the Gulf, we are proceeding with obtaining computerized database information on exogenous exposure, potentially using grid coordinates linked to modeling data from DoD. We have received information on unit locations during the Gulf War from the U.S. Army and Joint Services Environmental Support Group. Unit location information is being compiled and plans for analysis are being discussed.
In Year 3, we will conclude data collection and conduct data anlyses, with manuscript preparation to follow.

PUBLICATIONS

Proctor S, Wolfe J, Friedman M. Evaluation of health symptoms reported by Gulf War veterans. Paper presented at the Annual Meeting (9/94) of the International Society for Environmental Epidemiology, Research Triangle Park, North Carolina.

Wolfe J, Brown PJ, Bucsela ML. (1992) Symptom responses of female Vietnam veterans to Operation Desert Storm. Am J Psychiatry, 149, 676-679.

Wolfe J, Brown P, Kelley J. (1993) Reassessing war stress: exposure and the Gulf War. J Soc Issues, 49, 15-31.

Title Evaluation of Neurological Functioning in Persian Gulf Veterans

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC Boston

Study Start Date 10/1/94

Estimated Completion Date 9/30/99

Project Status Ongoing

VA-4B

Summary

OVERALL PROJECT OBJECTIVE: This study evaluates neurological functioning in returning Persian Gulf war veterans who present with nervous system signs and symptoms of the type described as "Gulf War Syndrome". This study uses sophisticated clinical neurophysiological techniques capable of detecting subtle changes in peripheral and central nervous system functioning: electroencephalography (EEG); evoked potential (EPs); nerve conduction studies (NCV) and functional magnetic resonance imaging (MRI).

SPECIFIC AIMS: The specific objectives of this study are: (1) to objectively describe Persian Gulf War veterans' neurological status using standard clinical methodology, (2) define to observe and determine patterns of central and/or peripheral nervous system deficits in the four designated diagnostic groups compared to controls, and (3) to explore whether similar patterns of particular exposure characteristics exist within the diagnostic groups and whether distinct patterns exist between the groups.

METHODOLOGY: Subjects are veterans from the subjects evaluated in Project 1 who have been diagnosed with disorders which have an hypothesized environmental trigger and include neurological complaints (presumed neurotoxicant encephalopathy, multiple chemical sensitivity, chronic fatigue syndrome and post-traumatic stress disorder). Approximately 300 subjects (200 selected cases and 100 controls) will be selected from Project #1 and examined over a five year period. Approximately 10 persons from each of the four diagnostic categories and 20 control subjects will be enrolled for study each year. These subjects will have a neurologic examination and questionnaire, EEG, EPs, and MR. Those subjects with presumed neurotoxicant encephalophy and those serving as controls also will have nerve conduction studies.

Since all subjects recruited for study are from subjects studied in Project 1, the groups are similar in age and gender distribution. Thus, subjects are not directly matched by gender and age with controls, but attention to these demographic factors will be made in selecting appropriate controls.

EXPECTED PRODUCTS (MILESTONES): In this study, we expect to determine if there are differences in subtle neurological functioning between veterans diagnosed with environmental health-related diagnoses of organic brain syndromes resulting from toxicant exposures, PTSD, MCS, or CFS compared to controls.

STATUS/RESULTS TO DATE: Electrophysiological testing of a cohort of PGW veterans is currently underway (n=50 clinical PGW patients). Our current plan is for the focus of the project to be on SPECT and MRI protocols, along with the nerve conduction study. Methodology and pilot studies to test the imaging methodology are currently in progress.

In light of recent DoD reports of sarin detection in the Gulf region during the war, we are considering the development of an appropriate evoked potential (EP) study protocol.

PUBLICATIONS none to date

Title Gulf War And Vietnam Veterans Cancer Incidence Surveillance

Research Focus: Miscellaneous
Research Type: Epidemiology Research
Agency VA
Study Location VAMC Boston
Study Start Date 10/1/94
Estimated Completion Date 9/30/99
Project Status Ongoing
VA-4C

Summary

OVERALL PROJECT OBJECTIVE: To examine the pattern of cancer diagnosed in Massachusetts Vietnam veterans as compared with Vietnam-era veterans for the time period 1988-1993. This linkage will be accomplished by linking a computer tape of Massachusetts veterans who received differential bonuses to the Massachusetts Cancer Registry master file and analyzing the resulting linked cases, as was done for the years 1982-1988 in prior study by the Principal Investigator. Another objective is to establish a database linkage for New England area Persian Gulf War veterans so as to be able to examine cancer incidence in this cohort at a later point in time.
SPECIFIC AIMS: 1. Monitor cancer incidence in Gulf War and Vietnam veterans of New England states, as part of the overall surveillance of disease in veterans exposed to environmental hazards; 2. Extend previous studies of cancer incidence and mortality by collecting and analyzing data on Massachusetts Vietnam veterans diagnosed in the years 1988-1993; 3. Analyze the results of the Massachusetts veterans cancer incidence linkage in a nested case-control design incorporating information on military and civilian occupations, branch of service and, where possible, location of service; 4. Establish a roster of Gulf War veterans in New England states, with identifying information such as names, dates of birth, and social security numbers, resulting in a computer file of Gulf War veterans that can be used in future linkage studies examining cancer incidence and mortality from various diseases; 5. Provide a database from which to plan additional clinical and preventative interventions to reduce morbidity and mortality from targeted diseases.
METHODOLOGY: In Year 1, we planned to initiate the linkage. In years 2-5, we plan to sort the cases into cancers of interest and other (auxiliary) cancers, analyze the data as a "nested" case-control study, and present odds ratios for specific cancers in Vietnam veterans compared with Vietnam-era veterans. Also in years 2-5, we plan to devise a system for linking the roster of Gulf War veterans in the New England states with cancer registries in all states which have population-based data.
EXPECTED PRODUCTS (MILESTONES): In this study we expect to determine cancer incidence rates in Massachusetts Vietnam veterans for the period 1988-1993. At completion of year 2 of the study, we expect to have preliminary results based on analysis of this database. Results pertaining to cancer incidence in Gulf War veterans is not expected for 10 years or so due to the latency period in cancer development.
STATUS/RESULTS TO DATE: The linkage program has been re-written and initial linkages run. Preliminary results have been obtained for the Massachusetts veterans bonus tapes linkage to the Massachusetts Cancer Registry. The mechanics for the linkages to the other New England Central Cancer Registries is in progress.

PUBLICATIONS none to date

Title Evaluation of Respiratory Dysfunction Among Gulf War Veterans

Research Focus: Environmental Toxicology

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC Boston

Study Start Date 10/1/94

Estimated Completion Date 9/30/96

Project Status Ongoing

VA-4D

Summary

OVERALL PROJECT OBJECTIVE: To assess respiratory status in relation to exposure to oil fire pollution in Gulf War veterans and evaluate the relationship between measures of pulmonary dysfunction and respiratory symptoms and exposure in subjects recruited for Project #1.
SPECIFIC AIMS: 1. Create a cumulative personal exposure estimate for each subject utilizing the U.S. Army Enviornmental Hygiene Agency exposure assessment data for their unit combined with geographic specific information which maps each unit's location in the Persian Gulf War theater; 2. Assess respiratory status using standardized respiratory questionnaire; 3. Assess respiratory function with physical examination and pulmonary function testing; 4. Assess pre-existing asthma risk with total serum IgE levels; 5. Assess non-specific bronchial responsiveness (BHR) as a measure of early outcome and as a potential risk factor in the development of lung disease by using methacholine challenge testing (initiating in Year 2 of the study); 6. Examine possible predictors of respiratory function (PFT's and methacholine challenge test) using cumulative environmental exposure assessment variable, respiratory medical history, occupational history, and smoking status variables; 7. Develop a database from which to plan preventative interventions to reduce morbidity and mortality from respiratory diseases.
METHODOLOGY: Subjects will be veterans from the subjects evaluated in Project 1. Each will complete a standardized respiratory questionnaire, systematic cardio-pulmonary physical exam, and pulmonary function testing. Spirometric measures will include forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC in accordance with American Thoracic Society recommendations. Subject data will be adjusted for age, height and gender and transformed to percentage predicted values using Knudson predictive equations. Blood will be drawn by venapuncture at the time of the visit and total serum IgE, complete blood count and differential and quantitative immunoglobulin levels will be measured. Additional blood samples will be drawn and stored for future laboratory tests (e.g., DNA analyses, infectious diseases). Bronchial responsiveness will be determined via methacholine challenge testing starting in Year 2. Nonspecific bronchial hyperresponsiveness has been suggested as a risk factor for, or an early event in the development of both acute and chronic occupational lung diseases. Occupational exposures to irritant substances at concentrations similar to the Gulf War exposures have been shown to cause airway hyperresponsiveness and it is believed that these exposures might be associated with the development of asthma.
EXPECTED PRODUCTS (MILESTONES): In this study, we expect to determine if there are differences in respiratory function (PFTs) in Gulf War veterans associated with cumulative personal exposure estimates obtained from exposure modeling by the U.S. Army Hygiene Agency. At the completion of Year 3 of the study, we expect to have preliminary results based on analyses of the data collected at that time.
STATUS/RESULTS TO DATE: To date, a total of 75 subjects have been recruited for the study. Blood samples are being collected and pulmonary function testing performed according to schedule. Methodology for methacholine challenge testing will be piloted and integrated into the existing study protocol in the fall of 1996.

PUBLICATIONS none to date

Title The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility

Research Focus: Environmental Toxicology

Research Type: Basic Research

Agency VA

Study Location VAMC Boston

Study Start Date 10/1/94

Estimated Completion Date 9/30/99

Project Status Ongoing

VA-4E

Summary

OVERALL PROJECT OBJECTIVE: The objective of this project is to test the hypothesis that the aromatic hydrocarbon receptor (AhR) is a molecular biomarker for polycyclic aromatic hydrocarbon (PAH) susceptibility. Veterans of the Persian Gulf war were potentially exposed to relatively high doses of PAHs in smoke emanating from Kuwaiti oil well fires. The high incidence of physical complaints by Gulf War veterans may reflect previously documented PAH toxicities including suppression of the immune system and neurologic dysfunction.
SPECIFIC AIMS: 1. Confirm that AhR expression levels correlate with PAH bioactivity; 2. Optimize the use of single strand conformational polymorphism (SSCP) analysis to detect AhR gene polymorphism and mutations in mice; 3. Apply results to human studies. Results obtained in the fulfillment of aims #1 and 2 will define the conditions for employing AhR levels and gene polymorphism as molecular biomarkers of PAH susceptibility.
METHODOLOGY: The first aim of the project is to confirm that the level of AhR in mice correlates with PAH toxicity and carcinogenicity. To do this first we propose genetically engineering AhR transgenic mice in which elevated AhR expression is directed to lymphocytes and then assessing a) PAH-induced immunosuppression as a representative indicator of organ toxicity and b) lymphocyte and lung transformation as measures of cancer risk in AhR transgenic mice.
To prepare for human studies, we will evaluate AhR polymorphism in mice using single strand conformational polymorphism (SSCP) analysis. Double stranded DNA from samples of veterans' blood is separated by heating followed by rapid cooling on ice. The three-dimensional conformation reassumed by each strand is determined by its nucleic acid sequence. Single nucleotide changes can be detected when the reannealed DNA is run on 6% acrylamide gels.
To apply results to humans, polyclonal and monoclonal antibodies to human AhR (and/or ARNT) will be produced and employed in conventional or PCR-based ELISAs of AhR protein levels in peripheral blood lymphocytes from Persian Gulf War veterans who complete Projects #1 and 4.
EXPECTED PRODUCTS (MILESTONES): This project will result in the production of new strains of mice which differ in their responsiveness to environmental pollutants. These mice will represent invaluable tools in investigating the effects of these pollutants in humans. We will also develop the technology to screen veterans of the Persian Gulf war for genetic factors which could put them at risk for immune defects and cancer.
STATUS/RESULTS TO DATE: As part of the first aim of this project we have successfully generated 8 chimeric mice, i.e., mice derived from both the normal cells of the blastocyst and from the blastocyst-injected embryonic stem cells. We are currently testing the ability of these stem cells to introduce the gene mutation into the germ line of these chimeric mice by breeding the chimeric mice with normal mice and looking for the transmission of the AhR mutation in the first generation. Germ line transmission of a mutated or overexpressed AhR transgene is essential to our studies. It is necessary to set up biologic assays to assess the effects of overexpressing the AhR gene in mutant mice. To this end we are setting up assays of immune responses in vivo (plaque forming cell assays, ELISA spot assays) and in vitro (Mishell/Dutton cultures). Antigens for these studies are being made and reagents required for the assays have been collected. (A microplate reader has been purchased and is being interfaced with a PC for rapid analysis of ELISA results.)
In order to quantitate the expression of AhR in mutant or in normal mice by western blotting and by novel ELISA techniques in aim #1, it is necessary to produce AhR-specific monoclonal antibodies. To this end we have expressed a full length AhR protein in a bacterial expression system, have

purified about 100 mcg of protein, and are preparing to immunize rats with the protein. In the meantime, we have developed an AhR ELISA assay with which to screen rat sera and putative hybridomas derived from immunized rats for anti-AhR antibodies.
In the proposal we have entertained the possibility that additional factors, e.g., ARNT accessory molecules, limit AhR activity. To prepare for this possibility, we have obtained anti-ARNT antibodies from a collaborator for western blotting analysis and have subcloned the murine ARNT gene for expression in bacterial systems. Purified ARNT will be used to generate monoclonal anti-ARNT antibodies as described for AhR. We have also set up collaborations to employ in situ hybridization and ligand binding assays to evaluate levels of AhR expression and function in transgenic mice.
In addition, we have been looking for genetic polymorphisms in the human AhR gene. After segmenting the gene into a ligand binding site and a DNA binding site and examining it using Sequence Specific Conformational Polymorphism techniques, we have found two alleles at each site, based on about 40 samples from the Center's veteran population (Project 4 subjects).

PUBLICATIONS none to date

Title Validity of Computerized Tests

Research Focus: Brain & Nervous System

Research Type: Clinical Research

Agency VA

Study Location VAMC Boston

Study Start Date 10/1/94

Estimated Completion Date 9/30/99

Project Status Ongoing

VA-4F

Summary

OVERALL PROJECT OBJECTIVE: The objective of this project is to continue the validation process of the Neurobehavioral Evaluation System (NES), a battery of computer-assisted behavioral tests developed for the purpose of detecting brain dysfunction secondary to exposure to neurotoxicants, with an expanded battery of subtests. The NES tests are derived from standard neuropsychological tests that have been well characterized in terms of brain-behavior relationships, but they differ in input and output modality and in other respects from traditional tests. Therefore, the validity of the NES subtests can only be verified by testing patients with known brain damage and showing that such damage affects performance on those tests. The sensitivity of the NES to neurotoxicant exposure cannot be fully interpreted, in terms of CNS mechanisms, without such validation.

SPECIFIC AIMS: 1. Assess the validity of the expanded battery of NES tests within the patient groups (Parkinson's Disease, Multiple Sclerosis, focal lesion patients) studied in the previous phase of this research. 2. Expand the validation study to include patients with other neurologic (Alzheimer's Disease, Huntington's Disease) and psychological disorders (PTSD), as well as those with conditions potentially induced by hazardous environmental or occupational exposure (MCS, CFS). 3. Correlate performance on the new NES subtests with performance on the standard paper-and-pencil tests on which they are based. 4. Determine the sensitivity of the NES subtests to the progression of neurologic disease by longitudinal testing of subject groups with deteriorating disorders.

METHODOLOGY: Neurologic subjects are being recruited from both the Boston VAMC and Boston University Medical Center. Subjects in the MCS, CFS and PTSD groups will be recruited from the population of Gulf War veterans assessed and diagnosed with these disorders in Project #1. PTSD diagnoses will be reviewed by Dr. Wolfe; MCS cases are being identified using criteria specified by Cullen (1987) and CFS cases are being identified using criteria specified by Fukuda et al., 1994. Each subject will have an initial interview to provide demographic data followed by adminstration of the Mini-Mental Status Examination and WAIS-R Information and Picture Completion subtests (40 minutes). Subjects meeting inclusion criteria will then be adminstered the expanded NES battery (approximately 100 minutes).

EXPECTED PRODUCTS (MILESTONES): This study has important clinical and research implications: (1) to facilitate the assessment of patients with suspected subtle brain damage secondary to exposure from neurotoxicants or from other diagnoses with a hypothesized environmental trigger (MCS, CFS, PTSD) by providing a sensitive, relatively brief battery of tests of CNS function that can be easily administered; (2) to provide a test battery for which brain-behavior relationships are known (providing measures which will then be useful in hypothesis-driven research on the cerebral localization of neurotoxicant effects); (3) to provide tests with known diagnostic validity for application to clinical situations. We expect to have preliminary results based on analyses of the data collected in the first years of the study, but the total project won't be complete for 3 more years.

STATUS/RESULTS TO DATE: Data analysis and manuscript writing have proceeded in Year 1 describing the validity of NES2 in various patient groups. The NES3 battery has been developed and is now being piloted.

PUBLICATIONS Krengel M, White RF, Diamond R, Letz R, Cyrus P, Durso R. A comparison of NES2 and traditional neuropsychological tests in a neurologic patient sample.

Neurotoxicology and Teratology 1996; 18:435-439.

White RF, Diamond R, Krengel M, Lindem K, Feldman RG: Validation of the NES2 in Patients with Neurologic Disorders. Neurotoxicology and Teratology 1996; 18: 441-448.

Title Health and Exposure Survey of Persian Gulf Veterans

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency VA

Study Location VAMC East Orange

Study Start Date 10/1/94

Estimated Completion Date 9/30/96

Project Status Ongoing

VA-5A

Summary

OVERALL PROJECT OBJECTIVE: To survey 2800 Persian Gulf War veterans randomly sampled from the Northeast quadrant of the U.S. to determine risk factors and their relationships to symptom clusters that could represent significant health problems for Gulf veterans.
SPECIFIC AIMS: 1. To provide health and medical histories of veterans who served in the Persian Gulf and veterans from the same period who were not deployed to the Gulf; 2. To characterize the medical and combat experiences of these veterans during the Gulf war; 3. To perform case control comparisons for various categories and combinations of symptoms with respect to individual and environmental risk factors identified in Aims 1 and 2.
METHODOLOGY: The survey will be mailed from Environmental Epidemial Service to veterans who served in the Gulf and those in the services at the time of the war but who remained stateside. This survey will be mailed to 2800 veterans on the Persian Gulf Registry. This survey will include a symptom checklist, an environmental risk factor survey, a family and social support survey, and anxiety and depression scales. Multivariate analysis of the resulting information will include cluster analysis, principal components factor analysis, and multidimensional scaling. From these analyses we expect to be able to develop one or more case definitions for the unexplained illnesses afflicting Persian Gulf veterans.
EXPECTED PRODUCTS (MILESTONES): We expect a high prevalence of Chronic Fatigue and Chemical Sensitivity in veterans with unexplained illness. We also expect to delineate a series of risk factors for the development of these illnesses, and for Post-traumatic Stress Disorder which may cluster with one or both of these illnesses. We expect these results to be available by the summer of 1996.
STATUS/RESULTS TO DATE: Data collection is almost complete. We have received 1,400 (57%) of our questionnaires back, and will close data collection on September 1, 1996 with a target of 60%. Symptom data has been preliminarily analyzed. At this point, 18% of the purposive sample returns meet 1988 criteria for CFS, 31% meet 1994 criteria for CFS, and 11% meet MCS case criteria. The mean number of endorsed symptoms out of 48 total was 24, with headaches, difficulty remembering, and fatigue being the most bothersome. Final analyses, incorporating risk factors, should be complete by January 1997.

PUBLICATIONS none to date

Title Physiological and Psychological Assessments of Persian Gulf Veterans

Research Focus: Immunology
Research Type: Clinical Research
Agency VA
Study Location VAMC East Orange
Study Start Date 10/1/94
Estimated Completion Date 3/1/97
Project Status Ongoing
VA-5B

Summary

OVERALL PROJECT OBJECTIVE: This project will determine if some of the unexplained medical illnesses in Persian Gulf veterans may be similar to Chronic Fatigue Syndrome or Chemical Sensitivity in civilian populations. It will include viral/immunological studies, neuropsychological studies, and studies of physiological responses to a number of physical and cognitive challenges. A series of psychosocial factors will be evaluated to determine whether they are risk factors for the illnesses suffered by these veterans. Because female veterans are overrepresented on the Persian Gulf registry in proportion to the number that served in the Gulf, we expect female veterans to make up half of our study subjects.

SPECIFIC AIMS: 1. To determine whether viral or cytokine patterns may suggest an infectious agent as a cause of illness in Persian Gulf veterans; 2. To determine if these veterans suffer chronic fatigue or chemical sensitivity; 3. To determine psychosocial risk factors that might have predisposed some veterans to develop their medical problems; 4. To determine if there are neuropsychological deficits in Persian Gulf veterans; 5. To determine if these veterans have abnormal physiological responses to physiological and cognitive challenges.

METHODOLOGY: Persian Gulf veterans that have chronic fatigue, chemical sensitivity, or a combination of these, and control era veterans not deployed to the Gulf will be recruited for these studies. Blood samples will be drawn, peripheral lymphocytes will be isolated, and polymerase chain reaction will be used to quantify herpes, epstein-barr and other viruses and to assess the level of interleukins and TNF-Â. The subjects (80/group) will fill out a series of psychosocial instruments and environmental exposure surveys. A battery of neuropsychological tests will be given in conjunction with an MRI. Finally, a series of challenges will be given including a tilt test, hand grip test, mild exercise on a stationary bicycle, and a cognitive stressor. Blood pressure, heart rate, cardiac output, expired CO2, and skeletal muscle blood flow will be assessed during and after these tests.

EXPECTED PRODUCTS (MILESTONES): We expect a number of the unexplained illnesses in Persian Gulf veterans will be similar to chronic fatigue syndrome and multiple chemical sensitivity. Our studies on civilians with chronic fatigue suggest that interleukins 6 and 7 and some of the herpes viruses might be elevated. We have also seen neuropsychological deficits in memory tasks and some decrease in white matter in the MRIs. Finally, we expect abnormal responsiveness to some of the physiological stimuli, but it remains unclear whether there will be hyper- or hyporesponsiveness.

STATUS/RESULTS TO DATE: Persian Gulf veterans seen here at the East Orange VA Medical Center were mailed a screening form to evaluate their suitability for entry into studies of chronic fatigue and chemical sensitivity. Additional veterans from an epidemiological survey of 2,800 Persian Gulf veterans in the northeast United States are now also being screened for entry into the studies in this project. To date, 48 subjects have been enrolled in our studies. (Based on screen form responses, 17 met criteria for CFS, 6 for MCS, 7 for both CFS and MCS, and 16 for healthy controls.) All studies on these veterans are progressing, but sufficient numbers for statistical analysis are not expected until the end of 1996. Final results from this project will be available in the summer of 1997.

PUBLICATIONS none to date

Title Effects of Exertion and Chemical Stress on Persian Gulf Veterans

Research Focus: Immunology
Research Type: Clinical Research
Agency VA
Study Location VAMC East Orange
Study Start Date 4/1/97
Estimated Completion Date 9/30/99
Project Status Ongoing
VA-5C

Summary

OVERALL PROJECT OBJECTIVE: This project will examine several hypotheses about the chronic fatigue and chemical sensitivity that may account for some of the unexplained illnesses in Persian Gulf veterans. Specifically, it will examine the maximum exercise capacity of these veterans compared to similar era veterans who were not deployed to the gulf. Following this, the physiological, immunological, and endocrine responses to a submaximal exercise test will be assessed. In another series of studies, double-blind controlled exposures to a chemical challenge will determine whether specific medical complaints, physiological responses, and cognitive impairments can be measured in chemically sensitive veterans. Because female veterans are overrepresented on the Persian Gulf registry in proportion to the number that served in the Gulf, we expect female veterans to make up half of our study subjects.
SPECIFIC AIMS: 1. To determine whether maximal exercise capacity is compromised in Persian Gulf veterans with chronic fatigue, chemical sensitivity, or a combination of these illnesses.
2. To determine whether the physiological, immunological, or neuroendocrine responses to a submaximal exercise are different in these veterans.
3. To determine whether object medical symptoms, immune responses, physiological responses, or cognitive impairments can be measured during double-blind exposures to a chemical challenge.
METHODOLOGY: The veterans with chronic fatigue, chemical sensitivity or both, as well a control era veterans who were not deployed to the Gulf (30/group), will be given a standard maximal exercise test on a treadmill and VO2max will be determined. Then, they will be given a submaximal exercise challenge at a relative work load during and after which blood sample will be drawn to assess cytokine responses, glucose and lactate responses, and adrenal stress hormone responses. The chemical challenges will be performed in the exposure chamber at the Environmental and Occupational Health Sciences Institute in Piscataway NJ. In order to perform double-blind exposures, the subjects will be given dermal exposures of phenylethyl alcohol (PEA), which is absorbed through the skin, in a situation where they cannot smell it. They will also receive a comparable inhalation dose to PEA. Autonomic arousal (blood pressure, heart rate), cognitive performance, nasal resistance, and markers of nasal inflammation will be measure before, during, and after exposure to PEA.
EXPECTED PRODUCTS (MILESTONES): In our civilian chronic fatigue patients, VO2max is slightly but significantly lower than sedentary controls, and we expect the same in Persian Gulf veterans with fatigue. We expect some abnormal responses to the submaximal exercise, but we are only now completing those studies in our civilian patients with fatigue. We also expect that veterans with chemical sensitivity will have greater responses to the chemical exposure than those that are not chemically sensitive.
STATUS/RESULTS TO DATE: Subjects are being recruited and evaluated through Project 2. Equipment for psychophysiologic monitoring has been purchased and installed. Pilot data for the neurobehavioral test and piloting of the psychophysiologic protocol is being collected. These are the last studies in the Environmental Hazards Research Center at the East Orange DVA Medical Center and are not planned to begin until 1997. There are no results to date.

PUBLICATIONS none to date

Title Effects of Genetics and Stress on Responses to Environmental Toxins

Research Focus: Pyridostigmine Bromide **Research Type:** Basic Research

Agency VA **Study Location** VAMC East Orange

Study Start Date 10/1/94 **Estimated Completion Date** 9/30/97

Project Status Ongoing VA-5D

Summary

OVERALL PROJECT OBJECTIVE: This project will determine whether genetic susceptibility to stress and exposure to chronic stress will result in persistent sensitization to potentially toxic effects of pyridostigmine bromide and aromatic hydrocarbons. In addition, it will examine the behavioral consequences of chronic exposure to these toxins.
SPECIFIC AIMS: 1. To expose WKY (stress-hyperresponsive) and SD (control) rats to chronic stress and then study the sensitivity to pyridostigmine bromide by measuring blood pressure responses and the sensitivity to aromatic hydrocarbons by measuring the activity of hepatic enzymes induced to metabolize these compounds.
2. To treat WKY and SD rats chronically with these compounds and examine behavioral rhythms, temperature rhythms, startle responsiveness, and neuroendocrine function (both basally and in response to stress).
METHODOLOGY: Sprague-Dawley (SD) and Wistar-Kyoto (WKY) rats will be implanted with chronic arterial catheters and then will undergo 3 days of a chronic stress regime. Twenty-four hours after the last stressor exposure, the blood pressure dose-response curves to pyridostigmine bromide will be determined in these rats and unstressed controls. In another set of similar animals, the neuroendocrine and brain c-fos responses to pyridostigmine bromide will be evaluated, as well as the levels of specific isozymes of cytochrome P-450 in the liver. These enzymes are responsible for the metabolism of a large group of xenobiotics, including aromatic hydrocarbons. The changes in these enzyme levels will also be evaluated following stressor exposures and subsequent exposure to aromatic hydrocarbons. Other sets of studies will determine the behavioral and some physiological effects of chronic treatment with pyridostigmine bromide and aromatic hydrocarbons, as well as their effects on the responses to chronic stress.
EXPECTED PRODUCTS (MILESTONES): We expect that chronic stress will persistently increase the sensitivity to pyridostigmine bromide, which might explain how a drug that is used extensively in civilian populations might become toxic under the stresses of the battlefield. We also expect that this effect will be more pronounced in WKY rats, which would show that genetic predisposition might explain why some veterans developed unexplained illnesses and others did not. We expect that hepatic P-450 levels will be inhibited more in WKY rats, and that these results could explain a greater sensitivity to toxins metabolized by these enzymes. Finally, we expect that chronic exposure to pyridostigmine bromide or aromatic hydrocarbons might show long-term effects on behavior or body temperature rhythms which could be very sensitive indices of chronic toxicity.
STATUS/RESULTS TO DATE: We have been unable to validate the behavioral hyperresponisveness in WKY rats that has been reported by others. However, startle responsiveness and open field activity have been much lower in WKY rats than SD rats, so we will continue to study these 2 strains. In addition, preliminary data suggest that pyridostigmine bromide may cause a substantial decrease in voluntary running activity in rats, but it is unclear as yet whether this could be a long-term effect. However, it is clear that WKY rats are more sensitive to some effects of pyridostigmine bromide that SD rats, but it remains unclear whether these effects will be long-term. These results have set the stage for the proposed studies of interactions among strain, chronic stress, and potential pyridostigmine bromide toxicity. This series of studies will be completed in the spring of 1997, and results will be available in the summer of 1997.

PUBLICATIONS none to date

Title Portland Environmental Hazards Research Center: Environment, Veterans Health and the Gulf War Syndrome. Core Project for Clinical and Epidemiology Research

Research Focus: Symptoms/General Health

Research Type: Epidemiology Research

Agency VA

Study Location VAMC Portland

Study Start Date 10/1/94

Estimated Completion Date 9/30/99

Project Status Ongoing

VA-6

Summary

OVERALL PROJECT OBJECTIVE: To illuminate the relationships between exposures (chemical, physical, stress) and unexplained illness in Gulf War veterans.
SPECIFIC AIMS: 1. To define caseness of unexplained illness in Gulf War veterans; 2. To develop a questionnaire of exposures and effects based on the results of veteran interviews and other relevant data; 3. To conduct a case-control study focused on the spatial-temporal relationship between exposures and illness; 4. To provide subjects for research conducted in Projects I, II and part of IV.
METHODOLOGY: An epidemiological study using a population-based case-control design is being implemented. Pilot work was conducted in two phases before final determination of the research protocol. The first phase consisted of fourteen open-ended interviews with veterans with varying degrees of health and diverse military exposures. The audio-taped interviews are each approximately 3 hours in length. Transcripts of the tapes were analyzed for themes related to knowledge of exposure to diverse chemical, biological, environmental, and psychological factors in the Persian Gulf. In addition, interviewees were asked to provide feedback on specific items being planned for inclusion in the final study questionnaire to promote comprehension and ease in response. The interviews were completed in the Spring of 1995.
The second phase of the pilot work was a feasibility study in which a sample of 422 subjects, randomly chosen from a data tape of Oregon and Washington residents serving in the Persian Gulf, were mailed a survey describing the proposed plan for the large epidemiology study. Specifically, the researchers sought information on potential response rates and barriers to participation. Modifications of the planned research protocol were made based on responses of the feasibility study.
The formal case control study began in November 1995. A random sample of veterans living in the Northwest will receive a mailed study questionnaire containing detailed information on exposures in the Gulf and current health status. The mailing of the survey questionnaire began in mid-November 1995, followed by the case-control clinical evaluations beginning in January 1996. The data base being used for the sampling frame was obtained from the DoD (Defense Manpower Data Center). The database contains the names/addresses of military personnel deployed to the Persian Gulf from August 1990 through July 1991, and listing Oregon or Washington as their home state of record. The accuracy of the addresses in the DoD database has been determined in the feasibility study. Arrangements were made with the Department of Veterans Affairs, NIOSH, and IRS to track individuals with invalid addresses in the DoD file. A small number of addresses have also been obtained from Equifax.
The survey methodology for year two of the funding period has been developed in consultation with Jim Bethel, PhD, Survey Statistician, Westat Inc. Out of approximately 3000 Oregon and SW Washington veterans, 1000 will receive questionnaires in 1995-96. Females and veterans in specific deployment groups (pre-combat, combat, post-combat) have been over-sampled. The first mailing wave to 387 veterans began in November 1995. Respondents to the first mailing wave will provide the selection pool from which the cases and controls agreeing to participate in clinical testing during the months of January-March 1996 will be drawn.
The working case working definition determined at the conclusion of the May 1995 Research Retreat with advisement from external advisory committee is as follows:
Must have at least one of the following signs or symptoms to be defined as a "Case". Onset must

be during or after deployment to the Persian Gulf. Symptoms must have persisted for one month or longer and have occurred during the three month period preceding the physical examination.

· Muscle/joint pain
· Cognitive changes including memory loss, confusion, inability to concentrate, mood swings, and/or somnolence.
· Diarrhea
· Skin or mucous membrane lesions
· Unexplained fatigue

Healthy controls and cases will be identified from responses to the mailed questionnaire. Cases and controls will be recruited for the medical workup at the Portland VAMC. Cases and controls participating in the clinical workup at the Portland VAMC will also serve as the subjects in Project I and II. In the future, subjects for Project IV will also be recruited from the Epidemiology Core subjects. Multivariant analyses will be conducted to compare subjects with unexplained illness and healthy subjects with respect to exposure to specific environmental factors.

The clinical protocols for the telephone recruitment, histories, physical examination, and testing to be completed on cases and controls have been approved by the Institutional Review Boards of OHSU and Portland VAMC.

EXPECTED PRODUCTS (MILESTONES): Definition of associations, and the strength of those associations, between exposures and unexplained illness

STATUS/RESULTS TO DATE: 1. Open-ended veteran interviews have been completed, transcribed, and summarized. Information gleaned from the interviews was incorporated in the questionnaire content.

2. Feasibility study completed on 422 randomly selected Oregon veterans in the population to be studied. Changes in the design have been implemented as a result of the findings:

A. Compensation of $10 will be given to all subjects that complete and return the mailed survey questionnaire.

B. The first year of survey mailing will focus on residents of Oregon. Initial mailing will be to 500 subjects randomly selected within a 50 mile radius of Portland. Subsequent mailings will be done to different geographic areas of the state. The final survey sampling will be representative of the geographic distribution of all potential subjects in the data base obtained from the DoD.

C. The mailing of questionnaires to potential subjects in areas outside of Portland will coincide with the negotiation of clinic space in VA facilities in outlying areas of the state. This change is necessary due to the proportion of subjects in the feasibility study that reported that they would not participate in the planned study due to the traveling time to Portland VAMC.

3. Survey sampling plan for 1995-1996 currently being implemented. Questionnaire returns are being scanned for data entry. Incomplete addresses are being tracked. As of August 15, 1996, an estimated 700 questionnaires have been mailed to veterans who served in the Persian Gulf war.

4. Clinical testing of subjects responding to mailed survey began in January 1996. As of August 6, 1996, 101 subjects have been evaluated in the case-control study.

PUBLICATIONS Shortridge LA, Joos S, Redmond, Spencer P, Bourdette D. Potential response bias in epidemiologic studies of Persian Gulf War veterans: American Journal of Public Health (Submitted)

Title Psychosocial, Neuropsychological and Neurobehavioral Assessment (Project I)

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC Portland

Study Start Date 10/1/94

Estimated Completion Date 9/30/99

Project Status Ongoing

VA-6A

Summary

OVERALL PROJECT OBJECTIVE: To determine if veterans have developed adverse neurobehavioral or psychological effects from service in the Persian Gulf War. If so, to determine the triggering events, including combat stressors, life stressors, chemical exposures, personality disorders, psychological health and motivation to seek compensation

SPECIFIC AIMS: 1. Determine whether veterans have psychological or stress-related disorders; 2. Determine the existence of a dose-effect relationship between neurobehavioral/psychological measures and unexplained illness; 3. Characterize neurobehavioral, neuropsychological, and psychosocial deficits in relation to Gulf War unexplained illness and illness associated with previous conflicts.

METHODOLOGY: Project 1 will determine if veterans of Operation Desert Storm (ODS) have developed any of a broad range of adverse health effects attributable to triggering events during their service in the 1991 Gulf War. The hypothesized triggering events: Combat or life stressors and chemical exposures. Potential factors that could contribute or influence the presence of adverse health effects will be assessed and entered into the analysis, including personality disorders, psychological health, medical conditions, and motivation to seek compensation.

Each veteran participating in the overall research program will receive a screening assessment with a 3-hour battery of 18 psychosocial, neuropsychological, and behavioral performance tests. The psychosocial and neuropsychological tests selected for the screening battery required lengthy administration times, offered a bewildering array of administration formats requiring individual explanation, and were in some cases poorly constructed. They have been implemented in a user-friendly and consistent computer-administration format that does not require individual explanation for each test. The entire battery will be piloted in 20-40 veterans to determine timing and acceptability of the final series of tests, and to assist in developing criteria/cut-off scores for selection of candidates for in-depth neuropsychological testing.

Based on screening exam performance, 25 "Cases" and 25 "Referents" per year will receive an in-depth clinical (neuropsychological) interview to more fully characterize apparent disorders. In addition, those initially demonstrating a high level of PTSD will be invited back after 1-2 years to repeat the tests to determine PTSD progression.

Results will be analyzed (a) by skilled clinicians (neuropsychological exam), (b) with multivariate techniques adjusted for confounders (neurobehavioral tests), and (c) with principal components analysis, logistic hierarchical multiple regression, discriminant function analysis, latent growth models analysis, and structural equation modeling to characterize the nature of the psychosocial results.

EXPECTED PRODUCTS (MILESTONES): Develop a predictive model relating the occurrence of unexplained illness to exposure factors.

STATUS/RESULTS TO DATE: Twelve valid, reliable psychosocial tests have been selected for administration in the 4-year cross-sectional study:

PTSD EVALUATION: Penn Inventory for PTSD, Mississippi PTSD Scale, PTSD Checklist; PSYCHOSOCIAL FACTORS: Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Substance Abuse Subtle Screen Inventory (SASSI), Life Experience Scale; PERSONALITY VULNERABILITY: Positive Affect Negative Affect Scale (PANAS), Minnesota Multiphasic Personality Inventory-II (MMPI-II); HEALTH SYMPTOMS: Health Status Questionnaire (SF-36), Hopkins Symptom Checklist (SCL-90R), WAR ZONE EXPERIENCE: Combat Exposure Scale,

revised (CES-r̄).
A common presentation format was developed for the 12 diverse psycholsocial and neuropsychological tests in order to improve acceptability and speed completion, using Supercard software for presentation on a Macintosh laptop computer. The new format includes a spoken test administration option (individually selectable and deselectable at any point in testing) which has been digitally recorded for inclusion with the test presentation system and options to navigate within a test to any question or to repeat the instructions. A training program was also developed to teach veterans to complete the questionnaires, and durable external Response Units (developed in a separately-funded project) have been connected to the laptop computers on which the tests are being presented to up to 8 veteans simultaneously (limited by space limitations). The new testing format (HHS) has been employed with 20 veterans and 10 civilians in pilot evaluations of the prototype training program. The responses from the test subjects were very positive about the testing system, and the mean questionnaire administration time approximated the target of 3 hours in a part of that group (Kovera et al., in press 1996). Changes recommended by respondents were introduced into the HHS. These tests are administered to all subjects tested by the Program's Core unit.
The neurobehavioral tests employed in this project were selected from the Behavioral Research and Assessment System (BARS): ATTENTION, MEMORY, AND LEARNING: Symbol Digit, Digit Span (forward and backward), Selective Attention Test, Serial Digit Learning; RESPONSE SPEED AND COORDINATION: Tapping, Simple Reaction Time; IMPAIRED MOTIVATION: Portland Digit Recognition Test (PDRT).
Most BARS tests were implemented under other funding to the PI of the project, but the PDRT and Tapping tests were prototyped and administered to pilot subjects for this project, including veterans involved in the psychosocial tests, above. The duration of testing met the target time of 60 minutes. These tests are administered to all subjects tested by the Program's Core unit. The test-retest reliability of the 19 tests in the new HSS and BARS computer-implemented formats in the order used in this project was assessed in 60 Oregonians during Summer, 1996.

PUBLICATIONS

Kovera CA, Anger K, Campbell KA, Binder LM, Storzbach D, Davis, KL, Rohlman DS. Computer-Administration of Questionnaires: A Health Screening System (HSS) Developed for Veterans. Neurotoxicology and Teratology (In press).

Anger WK, Kovera CA, Campbell K, Binder L. A Psychosocial and Neuropsychological Testing Format: the health screening system. Presentated at symposium on computerized behavioral testing of humans in neurotoxicology research; Portland, OR, 95

Title Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)

Research Focus: Immunology
Research Type: Clinical Epidemiology Research
Agency VA
Study Location VAMC Portland
Study Start Date 10/1/94
Estimated Completion Date 9/30/99
Project Status Ongoing
VA-6B

Summary

OVERALL PROJECT OBJECTIVE: Determine the relationship between exposures during the Persian Gulf War and the development of fibromyalgia.
SPECIFIC AIMS: 1. Screen veterans complaining of fatigue and musculoskeletal symptoms with previously developed and validated questionnaires and directed physical examinations to determine if fibromyalgia is present.
2. Correlate the presence or absence of fibromyalgia with possible environmental exposures, as determined in the core part of this program, or with neuropsychological factors, as determined in Project I: Psychosocial, Neuropsychological and Neurobehavioral Assessment.
3. Evaluate a smaller group of veterans with fibromyalgia and an age and sex matched group of veterans without fibromyalgia, for the neuroendocrine abnormalities described in fibromyalgia.
4. Repeat the clinical and neuroendocrine testing on the veterans with fibromyalgia (objective 3) 24-30 months after initial evaluation.
METHODOLOGY: Utilizing the cases determined in the case-control/epidemiological study, using validated methods, screen cases complaining of musculoskeletal complaints for fibromyalgia and controls without symptoms. Perform neuroendocrine testing on both cases and controls.
EXPECTED PRODUCTS (MILESTONES): 1. Determination of the association between exposure to the Persian Gulf War and the development of fibromyalgia; 2. Determine the prevalence of neuroendocrine findings in a primarily male sample; 3. Follow the course of the clinical/neuroendocrine findings with time.
STATUS/RESULTS TO DATE: The planning and coordination of the fibromyalgia study and the core epidemiological study have taken place in year-one. Andre Barkhuizen MD, Arthritis and Rheumatic Disease Fellow, has become the focal clinician responsible for integrating the fibromyalgia clinical study into the epidemiological case-control study. In addition to keeping abreast with national scientific work in the area of fibromyalgia and PGW veterans; preliminary work has consisted of reviewing the Portland Persian Gulf War registry for cases of musculoskeletal pain. The prevalence of complaints in the Portland sample is 29.6% compared to the national registry prevalence of 13.9% and the DoD Comprehensive Clinical Evaluation Protocol reported prevalence of 47%. Results from a pilot population-based survey of 157 veterans eligible for our epidemiologic case-control study indicate that the self-reported rates of musculoskeletal pain in both female and male subjects are both 38%. Responders to the mailed survey who have registered in the PGW registry are two times more likely to report musculoskeletal pain than responders who have not registered.
Investigators have worked closely with the epidemiological core in the development of the items to include in the survey questionnaire, telephone screening questions, and the history and physical examination to be done in the case-control study. Exclusionary diagnoses have been determined. The history and physical examination was pretested on three subjects with musculoskeletal pain in January 1996.
Since commencing the Persian Gulf Research Clinic in January 1996, the majority of subjects have been evaluated by a single examiner for rheumatological conditions. A blinded tender point examination is performed followed by a full rheumatology history and physical examination. The Core laboratory data which include an erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, rheumatoid factor, hepatitis B, C and human immunodeficiency virus serologies, and selected joint radiographs are reviewed at the bimonthly Clinical Case Review meeting to arrive at a final rheumatological diagnosis. Thus far 57 of the 80 subjects (71%)

admitted to some musculoskeletal complaint on direct questioning in the Persian Gulf Research Clinic. The following is a list of diagnoses (expressed as a percentage of the total clinic sample): mechanical backache 36%, myofascial pain 16%, fibromyalgia 14%, osteoarthritis 6%, tendinitis/bursitis 6%, hypermobility 5%, patellofemoral syndrome 3%, overuse syndrome 3%, inflammatory backache 3% and primary Raynaud's syndrome 1%. Only one subject had an inflammatory condition (a spondyloarthropathy). In 22 subjects (28%) two and occasionally three rheumatological diagnoses were made. In 10 male subjects (13%) with widespread musculoskeletal complaints no clear diagnosis could be made. The majority of subjects with musculoskeletal complaints were on no treatment and were in full-time employment.

In the majority of subjects the rheumatological laboratory investigations were normal. Two subjects had a positive antinuclear antibody (titer 1:80 and 1:320) without features of systemic lupus erythematosus. One subject without rheumatological complaints had a positive rheumatoid factor (titer 1:10). No subject had an elevated erythrocyte sedimentation rate or detectable C-reactive protein.

The second component of Project II entails the study of the neuroendocrine axis of the Persian Gulf veterans. All subjects attending the Persian Gulf Research Clinic are screened using the serum Insulin-like Growth Factor-I (IGF-1) and Insulin-like Growth Factor Binding Protein 3 (IGFBP3) levels. This has previously been shown to be reduced in 1/3 of patients with fibromyalgia. In the current study approximately one-third of the Gulf War veterans with fibromyalgia have low levels of IGF-1. Two of the 9 subjects with unexplained muscle and joint pain also have low IGF-1 levels. Further analysis of IGF-1 levels in asymptomatic veterans and those in the other "case" categories will be performed once sufficient numbers are reached.

The final component of the study involves evaluating changes in the neuroendocrine axis of subjects and will commence in August 1996. Twenty cases of fibromyalgia with low IGF-1 levels and twenty control subjects with normal IGF-1 levels will be admitted over the next 2 years for an in-depth study of their hypothalamic-pituitary-growth hormone and hypothalamic- pituitary-adrenal axis. The study protocol has been approved by a peer review committee of the Clinical Research Center – a dedicated research facility at the Oregon Health Sciences University, which is funded and regularly reviewed by scientists and clinicians from the National Institutes of Health. The laboratories of the Clinical Research Center and Oregon Graduate Institute will perform one-half hourly cortisol and growth hormone levels, a 24 hour cortisol production rate and two growth hormone stimulation tests. This will enable the research team to objectively document an altered neuroendocrine stress response and adult growth hormone deficiency in the symptomatic veterans. The altered neuroendocrine stress response will be correlated with the neuropsychological profile and particularly the stress scores collected by Project I. Finally, the stress response will be correlated with exposure to the various environmental agents and the deployment periods of the veterans, which is currently being collected in the Core epidemiology component of the study.

PUBLICATIONS

Burckhardt CS, Clark SR, Campbell SM, O'Reilly CA, Bennet RM. Events and co-morbidities associated with the onset of fibromyalgia. Presented at the International Myopian Meeting '95' San Antonio, Texas July 30-August 3, 1995.

Clark SR, Burckhardt CS, Bennett RM. Fibromyalgia patients improve oxygen consumption and pain score during a three month program of aerobic exercise. Presented at the International Myopian Meeting '95' San Antonio, Texas July 30-August 3, 1995.

Bennett RM. "The Fibromyalgia Syndrome" in Textbook of Rheumatology, 5th Edition, Ed. J. Kelly, Harris, Ruddly and Sledge. Ed. DL Goldenberg (In Press).

Title Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)

Research Focus: Pyridostigmine Bromide **Research Type:** Basic Research

Agency VA **Study Location** VAMC Portland

Study Start Date 10/1/94 **Estimated Completion Date** 9/30/99

Project Status Ongoing VA-6C

Summary

OVERALL PROJECT OBJECTIVE: To evaluate the neurotoxic potential of a group of hydrocarbon solvents and the effects on cholinergic neurons of long-term exposure to pyridostigmine bromide (PB).
SPECIFIC AIMS: 1. To evaluate effects of pyridostigmine bromide (PB) on cholinergic function in cerebellar and spinal cord explants. 2. To identify the cellular targets of neurotoxic hydrocarbon solvents. 3. To examine the relationship between the chromogenic and neurotoxic properties of selected organic solvents.
METHODOLOGY: Spinal cord-dorsal root ganglia (DRG)-muscle cultures derived from fetal mice are used to study to effects of chronic and acute exposure to pyridostigmine on cholinergic function. Cerebellar cultures derived from newborn mice are used to study the relationship between chromogenic and neurotoxic properties of a group of monocyclic and dicyclic hydrocarbon solvents. The substances to which cultures will be chronically exposed are directly incorporated into the culture medium. The dosage and duration of exposure to pyridostigmine and each of the solvents will be experimentally determined.
Morphological Analyses; Control and treated explant cultures will be stained with thionin (for Nissl substance). This stain allows the evaluation of the various neuronal cell groups present in explant cultures by light microscopy. Central and peripheral myelination can be readily examined in the living state using bright field optics. Immunohistochemical staining will be used to identify alterations of specific neural components (neurofilaments, calbindin), neurotransmitters (choline acetyltransferase, acetylcholinesterase) and supportive glial cells (glial fibrillary acidic protein) induced by neurotoxic compounds. Synaptic changes will be elucidated by electron microscopy.
Electrophysiology; In spinal cord-DRG-muscle explants, extracellular electrodes are used to record dorsal horn, ventral horn and muscle responses evoked by extracellular stimulation of dorsal and ventral roots. In cerebellar cultures, neurons develop spontaneous activity as they mature in vitro. Extracellular recordings are used to obtain single unit discharge rates and, in combination with extracellular stimulation, are used to assess the efficacy of excitatory and inhibitory synaptic circuitry. Intracellular electrodes are used to study the active and passive properties of individual neurons (motorneurons in the spinal cord cultures and Purkinje cells in cerebellar cultures) and their synaptic responses to afferent stimulation.
Data Analysis; The statistical significance of quantitative data will be evaluated by one way analysis of variance (ANOVA) for each treatment followed by the Tukey HSD (honestly significant difference) test for multiple comparisons, if the data are normally distributed and have equal variances. If the data do not follow a normal distribution, then the nonparametric Krustal-Wallis test followed by a Mann-Whitney U test will be used for statistical analysis. All statistical evaluation will be done using Systat computer software (SPPS Inc., VA).
EXPECTED PRODUCTS (MILESTONES): Electrophysiological and morphological characterization of the cellular neurotoxicity of selected hydrocarbon solvents and pyridostigmine bromide
STATUS/RESULTS TO DATE: Early results have shown that acute application of PB to spinal cord explants co-cultured with skeletal muscle enhances muscle contractions. This effect is consistent with PB inhibition of acetylcholinesterase and greater availability of acetylcholine at the neuromuscular junction. Long-term exposure of spinal cord explants co-cultured with skeletal muscle causes a progressive decrease of muscle contractions and sensitivity to acetylcholine. Additional morphological and electrophysiological studies are in progress to examine effects of long

term exposure to PB on the neuromuscular junction. Experiments to evaluate the neurotoxic potential of the bromide anion using the same in vitro preparation are also in progress. To date, no noticeable changes in neuromuscular function have been observed following long term exposure (2 weeks) to 10-6 M sodium bromide.

PUBLICATIONS Drake-Baumann, R. and F.J. Seil. (1996). Effect of long term anticholinesterase exposure on neuromuscular function in vitro. Soc. Neuroscience Abst. (in press).

Title DNA Damage from Chemical Agents and Its Repair (Project IV)

Research Focus: Environmental Toxicology

Research Type: Basic Research

Agency VA

Study Location VAMC Portland

Study Start Date 10/1/94

Estimated Completion Date 9/30/99

Project Status Ongoing

VA-6D

Summary

OVERALL PROJECT OBJECTIVE: Determine the long-term consequences of genotoxin exposure on the nervous system of veterans. Of specific interest are nitrogen mustards --- used here as surrogates for sulture mustard chemical warfare agents.
SPECIFIC AIMS: 1. Determine the type and quantity of specific DNA adducts and the capacity to repair these adducts in control and nitrogen mustard (NH2) treated genomic DNA isolated from normal human skin and brain; 2. Determine the type and quantity of specific DNA adducts and the capacity to repair these adducts in genomic DNA isolated from mouse cerebral cortex cultures treated with NH2; 3. Assess the relationship between DNA damage, DNA repair and cell degeneration in mouse cerebral cortex cultures treated with nitrogen mustard (NH2); 4. Compare and contrast DNA damage, DNA repair and cytotoxicity in primary neuronal and primary glial cultures treated with nitrogen mustard (NH2).
METHODOLOGY: Human skin and murine cortical explant cultures will be used to determine the effect of nitrogen mustard (mechlorethamine, NH2) on genomic DNA. Human skin and mouse cortical explants will be treated for up to 4 days with NH2, genomic DNA isolated from control and treated explant tissue, and the DNA analyzed for adducts by 32P-postlabeling. For comparative purposes, different nervous tissue cell types (neurons, astrocytes) will be treated with NH2 to determine the relative sensitivity (DNA damage, cytotoxicity) of specific cells to NH2 in the nervous system. Findings from these studies will be important for establishing a possible relationship between DNA damage, genotoxin exposure and cytotoxicity of nervous tissue.
EXPECTED PRODUCTS (MILESTONES): 1. We will know whether veterans from the Gulf War have been exposed to chemical agents based upon comparisons between skin tissue obtained from Gulf War veterans and military personnel not engaged in active duty (Biomarkers of previous exposure to a genotoxin); 2. The health status of veterans with regard to their DNA repair profile (protein levels and activity); 3. If chemical warfare agents can induce long-term damage to nervous tissue and produce a spectrum of behavioral symptoms much like those experienced by Gulf War veterans.
STATUS/RESULTS TO DATE: Viability Studies - In vitro cytotoxicity studies were begun to determine if CNS cell types are differentially sensitive to mustards (NH2). Primary rat cortical astrocyte cultures were treated with various concentrations of mechlorethanamine (NH2). Initial studies indicated that NH2 was toxic to astrocyte cultures (80% confluency) at concentrations > 50 µM for 1h. In contrast, brief exposure (30 min) of astrocyte cultures to 100 µM NH2 media and replacement with control media resulted in minimal damage to astrocytes after 24 h. Lower concentrations of NH2 (0.1-1.0 µM) for 24 h produced minimal damage to astrocytes following incubation of treated cultures with the vital fluorochrome dyes propidium iodide and rhodamine 123 and examined for cytotoxicity by fluorescent microscopy. Astrocytes were more sensitive to low concentrations of NH2 than human melanoma cells and murine lymphoid cells;
As of August 1996, we have 1) Began study of the response of rat glial cells to nitrogen mustard. Cells proved to be less sensitive to mechlorethamine than human melanoma or murine lymphoid cell lines. 2) Detection of DNA adduct 06-methylguanine by immunocytochemical and mass spectrometric techniques. 3) Developed assay for alkyl guanine transferase, a specific repair protein for one type of DNA damage. 4) Probed rat brain for DNA-repair protein levels and activity following treatment with nitrogen mustard. 5) Developed assays for measuring the predominant nitrogen mustard-induced DNA adduct (N7-hydroxyethyl guanine, a monofunctional adduct) and

cross-links (difunctional adducts). Obtained authentic N7-hydroxyethyl guanine adduct from Dr. Mark Marino of Walter Reed Hospital to measure this adduct by chromatographic methods. 6) Examined the acute (24 h) and long-term (7 day) cytotoxic effect of nitrogen mustard on human skin tissue (SKIN2). HN2 is acutely toxic to human skin tissue at high concentrations but extensive tissue damage can be induced by concentrations that are 1/10 or 1/100 of the acute dose when tissue is exposed for long periods of time. 7) APE expression (levels and activity) in neuronal and human skin cultures is modulated by HN2. APE levels increased in HN2-treated rodent neuronal cultures (non-dividing cells) while APE levels decreased in human neuronal cultures (dividing cells). APE activity increased in HN2-treated human skin cultures (actively dividing cells). Altered levels and activity of APE may be an indication of HN2-induced DNA damage.

PUBLICATIONS Kisby GE, Sweatt, Spencer PS (1995) Role of DNA repair in protecting mature nervous tissue from DNA damage. J Cell Biochem 21A, 348.

Title Desert Storm Reunion Survey

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC Boston

Study Start Date 4/1/91

Estimated Completion Date 9/30/95

Project Status Complete

VA-7

Summary

OVERALL PROJECT OBJECTIVE: The Ft. Devens ODS Reunion Survey represents a longitudinal assessment of readjustment of Persian Gulf War veterans returning through Ft. Devens, Massachusetts following their return from the Gulf region.
SPECIFIC AIMS: 1. Describe troop demographics of the Ft. Devens cohort of Persian Gulf War veterans.
2. Examine, both cross-sectionally and longitudinally, family and unit support factors, war-zone exposure, PTSD and pyschological distress symptomatology in these veterans.
3. Examine physical health status at Time 2 and explore potential risk factors important in the development of adverse physical health after return from a wartime environment.
METHODOLOGY: Subjects were recruited from a group of appoximately 5000 Persian Gulf War veterans who returned home through Ft. Devens, Massachusetts after the Gulf War. The survey at Time 1 constituted a broad range of demographic questions accompanied by an assessment of Post-Traumatic Stress Disorder (PTSD) symptomatology (Mississippi Scale for Combat-related PTSD; Keane, Cadell & Taylor, 1988), general psychological well-being (Brief Symptom Inventory, BSI; Derogatis & Melisaratos, 1983), and combat exposure (Gallops, Laufer & Yager 1981; Rosenheck, 1992), along with queries of other relevant domains including change in work status, current family and social functioning, and post-deployment major life stressors (e.g., death of a loved one, separation or divorce, loss of property, physical or sexual assault) and at Time 2, additional questions were added to further assess psychological health and physical health symptoms. Individual health symptoms were assessed using the 20-item Health Symptom Checklist (Bartone et al., 1989) which asked subjects to indicate the presence and frequency of symptoms over the past several weeks using Likert-type ratings (0=none, 1=a little, 2=often, 3=very often). In addition, subjects were asked to rate their current physical and psychological health separately ('poor', 'fair', 'good', 'very good' or 'excellent') as well as to rate changes in their physical and psychological health since return from the Persian Gulf ('much worse', 'worse', 'same', 'better' or 'much better').
EXPECTED PRODUCTS (MILESTONES): Data from this investigation is expected to provide an important opportunity to examine patterns of readjustment and the factors that contribute to the changes in the years soon after return from a wartime environment. Results from analyses of Time 1 and Time 2 collected data have been published. Publications in progress include evaluation of reported health symptoms by this cohort of Persian Gulf War veterans at Time 2, examination of reported sexual harassment by the women surveyed, and a longitudinal assessment of PTSD and psychological symptomatology between Time 1 and Time 2.
STATUS/RESULTS TO DATE: Over 84 U.S. Army units (n=2949) were surveyed immediately upon their return to Ft. Devens, Massachusetts (Time 1) between April and July 1991. Persons tested at Time 1 represented approximately 60% of the troops that were deployed to the Gulf from that base, and comparisons between this sample and data available for the Ft. Devens military population at large indicate that survey respondents are generally representative of the base's military population. Examination of nonparticipants at Time 1 indicated random absences for administrative and medical purposes. The original cohort contained 2,709 men and 240 women with a mean age of 30.2 years (SD = 8.6) and 13.2 years of education (SD = 1.8). The majority of troops were Caucasian (87.4%) and reservists (52.2% National Guard; 19.9% Army reservists; 27.9% active duty). Active duty troops had more black members and were significantly younger in

age compared to Guard and Reserve Troops. Overall, veterans in the original cohort do not fully reflect military assignments or ethnic and gender compositions of the total U.S. Army or Gulf force (U.S. Government Accounting Office, 1992; communication with Defense Manpower Data Center). Consistent with the Ft. Devens' mission, a higher than average proportion of the original sample had combat support and service support positions during the war, rather than active combat roles. Approximately 18-24 months after initial testing, veterans were resurveyed (Time 2) to reevaluate their adjustment. This survey repeated all Time 1 measures and queried other relevant domains including work status, family and social functioning, health status, health service use, and intervening life stressors. In the majority of cases, the Time 2 survey was readministered in persons during weekend unit drills. Persons in units that could not be scheduled in a timely fashion were resurveyed using an identical questionnaire sent through the mail. A total of 2,313 persons successfully completed the Time 2 survey (2,119 men, 194 women; Wolfe et al., 1993), yielding an overall response rate of 78%. Analyses of these data show no significant Time 1 differences between Time 2 respondents and non-respondents on most background or outcome measures (e.g., educational level, PTSD symptomatology). However, individuals who did not complete the Time 2 reevaluation were more likely to be younger and on active duty status. Based on veterans' verbal and written comments concerning their health status at Time 2, the Time 3 investigation (now Project #1 of the Boston Environmental Hazards Center) was designed to reexamine overall adjustment with a special emphasis on physical health and psychological status and to evaluate cognitive functioning by neuropsychological test methods on a subset of the larger cohort.

PUBLICATIONS

Wolfe J. Preliminary report of reunion survey on Desert Storm returnees. In. R. Rosenheck, et al. (eds.). War-zone stress among returning Persian Gulf troops: A preliminary report. Legislative report to Congress. 1991.

Wolfe J, Kelley JM, Buscela ML, Mark WR. Ft. Devens Reunion Survey: Report of Phase I. In R. Rosenheck et al. (eds.), War-zone stress among returning Persian Gulf troops: Final Report. Legislative report to Congress. 1992.

Wolfe J, Brown PJ, Kelley JM. Reformulating war stress: Exposure and the Persian Gulf War. Journal of Social Issues, 49, 15-31. 1993.

Title Psychological Test Data of Gulf War Veterans Over Time

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC Mountain Home

Study Start Date 7/9/91

Estimated Completion Date 3/30/97

Project Status Ongoing

VA-8

Summary

OVERALL PROJECT OBJECTIVE: (1) To learn more about reactions to combat exposure, stress, and Persian Gulf War-related health concerns, (2) exploration of the relationships among symptoms, demographic variables and veterans' psychological status, (3) to provide intervention, education, and support to Gulf War veterans by providing a) general information about reactions to combat/desert duty, and b) opportunities for individual discussion of experiences and current physical health, (4) administration of standardized psychological questionnaires and instruments, and (5) referral to VA and other community services available for health and other related concerns.
SPECIFIC AIMS: To learn more about psychological stress and physical symptoms experienced by Persian Gulf War veterans.
METHODOLOGY: Initially evaluated 66 gulf War Marine reservists on a number of psychological instruments within 5 months of Operation Desert Storm using the Mississippi Scale for Desert Storm War Zone Personnel, MMPI-2, Impact of Event Scale, War Stress Inventory-Operation Desert Storm Version, Rorschach test evaluation of DSM-III-R criteria for post-traumatic stress and post-traumatic stress disorder (PTSD). At one year follow-up, the MMPI-2 and Impact of Event Scale were collected on a sub-sample of these Gulf War veterans. At 3-year follow-up, all of the original measures, plus a physical symptom questionnaire selected questions from the Persian Gulf Registry Code Sheet and The Hand Test, were administered to a sub-sample of the original group and a control group of Marine Reservists from the same unit who had never been stationed outside of the U.S. Statistical analyses employed in this study included correlation, paired and independent t-tests, ANCOVA, MANCOVA, discriminant analysis, stepwise discriminant analysis, and repeated measure design ANOVA. Currently, volunteers referred for psychological and neuropsychological evaluation will complete all the measures listed above, the Halstead-Reitan Neuropsychological Test Battery, and questions related to disability status.
EXPECTED OUTCOMES: Assess the utility of psychological instruments in the detection of war-zone stress reactions. Instrument variables associated with response to stressors are expected to be related to DSM-III-R criteria for post-traumatic stress and PTSD.
STATUS/RESULTS TO DATE: The project is currently ongoing, the sample size is increasing and data are being collected. Results to date show differences over time between the initial evaluation data and follow-up, and between initial evaluation and control group on selected variables associated acute distress, and capacity for coping. Findings are being analyzed in relation to the assessment, understanding, and treatment of post-traumatic stress symptomology of PTSD.

PUBLICATIONS

Sloan P, Arsenault L, Hilsenroth M, Harvill L, Handler L. (1995). Rorschach measures of post-traumatic stress in Persian Gulf War veterans. Journal of Personality Assessment, 64, 397-414.

Sloan P, Arsenault L, Hilsenroth M, Harvill L, Handler L. (1996). Rorschach measures of post-traumatic stress in Persian Gulf War veterans: A 3-year follow-up study. Journal of Personality Assessment, 66(1), 54-64.

Sloan P, Arsenault L, Hilsenroth M, Harvill L. (1996). Assessment of non-combat, war-related post-traumatic stress symptomatology: validity of the PK, PS, and IES Scales. Assessment, (3)1, 37-41.

Title Evaluation of Cognitive Functioning in Persian Gulf War Veterans Reporting War-related Health Problems

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC New Orleans

Study Start Date 4/1/94

Estimated Completion Date 9/30/95

Project Status Completed

VA-9

Summary

OVERALL PROJECT OBJECTIVE: Addressing a topic of timeliness and importance, this project evaluated cognitive and psychosocial functioning among Operation Desert Storm (ODS) veterans who experienced health problems and physical symptoms following return from the Persian Gulf War zone. The primary objective of the project is to explore environmental, neurotoxic, and psychological correlates of health complaints among these veterans.

SPECIFIC AIMS: The project examined potential differences between veterans reporting high levels of health concern and those reporting low levels of concern on measures of psychological well-being, psychopathology, environmental exposure to toxins and adverse environmental events in the war-zone and prior to war-zone duty, and neuropsychological functioning.

METHODOLOGY: Conducted in cooperation with a research team of psychologists working at the Boston VAMC, study design incorporated a local sample of 78 Persian Gulf returnees who were divided into high and low health concern subsets on the basis of self-reported health status. Participants underwent a clinical diagnostic evaluation that includes administration of an environmental exposure interview; a structured psychodiagnostic interview; a battery of neuropsychological tests selected for their specificity and sensitivity to neurotoxicity and emotional and motivational factors; and self-report inventories assessing mood, emotional well-being, PTSD symptomatology, combat exposure, and physical symptoms. Statistical analysis incorporated a multivariate analysis of variance approach, comparing the two health concern subgroups from both sites on measures of environmental exposure, psychological and neuropsychological functioning, and physical symptoms.

EXPECTED PRODUCTS (MILESTONES): Given current interest in the multiple, yet inadequately diagnosed or explained health problems and symptoms reported by sizable subsets of returnees from the Persian Gulf War, this project will have direct relevance to health care delivery in the VA system nationwide. Study results will be pertinent to development of appropriate clinical diagnostic and treatment services for Persian Gulf returnees and veterans of more recent military operations and objective evaluation of veteran disability and compensation claims in the VA system.

STATUS/RESULTS TO DATE: Data collection at New Orleans site has been completed. All data have been forwarded to the Boston site for multi-site statistical analysis.

PUBLICATIONS none to date

Title Memory and Attention in PTSD

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC New Orleans

Study Start Date 2/1/94

Estimated Completion Date 9/30/98

Project Status Ongoing

VA-10

Summary

OVERALL PROJECT OBJECTIVE: Clinical reports have documented that as many as 67-100% of veterans undergoing treatment for war-related post-traumatic stress disorder (PTSD) exhibit deficits in memory and concentration. This project seeks to address the common and potentially debilitating problems of impaired learning, memory, and attention functions reported by veterans suffering PTSD.

SPECIFIC AIMS: Incorporating two separate investigations, this research applies a comprehensive assessment protocol that includes evaluation of psychopathology and neuropsychological functioning in veterans of Vietnam and a younger cohort of Persian Gulf returnees. In particular, the project will provide in-depth description and analysis of learning, memory, and attention functioning among these veterans.

METHODOLOGY: Within each study, comparisons of neuropsychological performances are conducted between community-recruited groups of veterans with PTSD diagnoses related to war-zone duty, veterans with diagnoses of depression, and veterans found to be free of psychopathology. Psychopathology is assessed with structured clinical interview and self-report inventories. Attention, learning, memory, and other cognitive processes are assessed with standardized neuropsychological assessment instruments. Data analysis, conducted separately for the two cohorts, are accomplished using a multivariate of analysis approach.

EXPECTED PRODUCTS (MILESTONES): Because problems with attention, learning, memory, and other cognitive functions can dramatically disrupt social and occupational functioning, as well as hinder treatment efforts of war-related stress and other disorders, studies of neuropsychological sequelae to war trauma are pivotal to understanding the complex behavioral and emotional expression of PTSD, to delivery of appropriate, effective treatment interventions to these veterans, and to exploring long-term psychosocial outcomes in veterans suffering PTSD and served by the VA system.

STATUS/RESULTS TO DATE: To date, this newly funded research has been conducted on a sample of 95 Persian Gulf returnees. Findings reveal that in comparison to psychopathology-free veterans, veterans diagnosed with PTSD performed significantly more poorly on verbal intellectual tasks including those tasks thought to predict premorbid functioning. Results suggest that intellectual resources, particularly verbal skills, may buffer development of stress-related psychopathology following trauma exposure. Analysis of cognitive data reveal specific deficits in sustained attention, working memory, initial acquisition of new material, and resistance to retroactive interference. Collection of data with Vietnam veterans is ongoing.

PUBLICATIONS none to date

Title Neuropsychological Functioning in Veterans

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC New Orleans

Study Start Date 2/1/92

Estimated Completion Date 3/1/95

Project Status Complete

VA-11

Summary

OVERALL PROJECT OBJECTIVE: Complaints of impaired memory and concentration among veterans seeking treatment for post-traumatic stress disorder (PTSD) highlight the importance of systematic evaluation of these cognitive functions among PTSD-diagnosed veterans. The primary objective of this project was to collect pilot data regarding learning, memory, and attention functioning in Persian Gulf returnees reporting PTSD symptomatology.
SPECIFIC AIMS: The specific aim of this project was to compare learning, memory, and attention performances in samples of Persian Gulf returnees with and without diagnoses of PTSD.
METHODOLOGY: Subjects were 15 Persian Gulf War zone veterans diagnosed with military-related PTSD and 27 Persian Gulf War zone veterans found to be free of any PTSD symptomatology. All subjects underwent structured psychiatric interview and neuropsychological assessment using a brief screening battery designed to emphasize attention, learning, and memory functioning. Statistical analyses included a series of univariate analyses of variance (ANOVAs) and univariate analyses of covariance (ANCOVAs) using vocabulary performance as a covariate to compare the two samples on demographic variables and dependent measures of cognitive functioning.
EXPECTED PRODUCTS (MILESTONES): Results of this project impact potentially on comprehensive assessment and treatment services provided to PTSD-diagnosed Persian Gulf War zone veterans.
STATUS/RESULTS TO DATE: Veterans in the PTSD sample were on average older, less educated, and performed more poorly on a vocabulary task used as an estimate of premorbid intellectual sophistication than veterans in the comparison sample. Comparisons of group performances on the neuropsychological tasks revealed that the PTSD sample performed more poorly than the comparison sample on measures of simple and complex attention and word retrieval. When differences in estimated native intellectual skills were controlled for statistically by the inclusion of vocabulary performance as a covariate in a series of ANCOVAs, no significant differences between groups emerged on any of the attention or memory measures. That the effects of PTSD on attention and memory functions could not be parceled out from those attributable to such factors as lower levels of education and premorbid intellectual sophistication does not negate the clinical significance of study findings. Results of this exploratory pilot project complement previous research suggesting that higher levels of education and intellectual functioning may buffer the impact of trauma on the development of subsequent stress-related psychopathology. This phase of the project is complete and has led to the development of a more refined and comprehensive neuropsychological protocol to be administered to a larger sample of Persian Gulf veterans.

PUBLICATIONS

Vasterling JJ, Root L, Brailey K, Uddo M, Sutker PB. Attention and Memory performances in post-traumatic stress disorder. Paper presented at 22nd Annual Meeting of the Internat. Neuropsychological Society, Cincinnati, OH. February 1994.

Title Psychological Assessment of Operation Desert Storm Returnees

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC New Orleans

Study Start Date 8/1/91

Estimated Completion Date 9/1/97

Project Status Ongoing

VA-12

Summary

OVERALL PROJECT OBJECTIVE: This research was designed to determine the psychological sequelae to war-zone exposure among troops who served in the Persian Gulf during Operation Desert Storm (ODS) compared to troops who were activated during ODS but not deployed to the Persian Gulf.

SPECIFIC AIMS: Objectives of this project are to conduct comprehensive psychological assessments and debriefings among the masses of troops mobilized in support of ODS; identify psychological, somatic, and cognitive symptoms and mental disorders, both early and persistent, that are associated with Persian Gulf war-zone exposure; and explore person resource and environment factors that may differentiate Persian Gulf-deployed troops exhibiting war related psychopathology from troops found to be free of psychological disturbances.

METHODOLOGY: Comprehensive psychological assessments were conducted with non treatment seeking troops who served in the Persian Gulf and a comparison sample of troops from the same military units who were activated during ODS but not deployed to the Persian Gulf. Follow up assessments continue for up to five years to assess psychological status over time and ongoing symptomatology. The subject sample to date includes 1520 military personnel mobilized in support of ODS, including 517 Louisiana National Guard and 1003 Marine, Army, Air Force, and Navy Reserve troops, 194 of whom were members of Quartermaster units assigned graves registration duties. Subjects reported an average age of 29 years at time of initial assessment and completed an average of 13 years of formal education. The percentage of African American and other minority troops was 43%, and 14% were women. An assessment battery tapping domains of personal resources, stressor characteristics, negative mood states and traits, psychiatric and physical symptoms, and symptoms of posttraumatic stress disorder (PTSD) was administered in regularly scheduled drill exercises at 6, 8, and 12 months following ODS and at one year follow up intervals. An individually administered comprehensive structured clinical diagnostic interview was conducted with a subset of graves registration troops judged to be at high risk for negative psychological sequelae because of their gruesome Persian Gulf body handling duties. Data analytic strategies for continuous variables included multivariate and univariate analyses of variance, with repeated measures where indicated, and stepwise discriminant function analyses. Chi square analyses were conducted for categorical variables.

EXPECTED PRODUCTS (MILESTONES): By establishing prevalence estimates for negative sequelae to war-zone duty, identifying troops at high risk for development of war zone related psychopathology, and determining factors associated with increased psychological vulnerability to war zone service, results have implications for development of more effective and efficient strategies and procedures for military training and preparing troops for war zone exposure, conducting debriefing exercises to facilitate community reentry following war zone service, and providing mental health treatment interventions specific to war zone related psychopathology.

STATUS/RESULTS TO DATE: The project is ongoing, with follow up assessments planned for five years following initial evaluation and debriefing. Comparisons of data collected upon initial assessment among 876 war zone deployed and 396 non war zone deployed troops showed that troops exposed to war zone duty reported higher levels of depression, anxiety, and somatic preoccupations than did the non war zone deployed sample. Specifically, 23% of the war zone deployed sample showed at least mild levels of clinical depression, and 14% met criteria for PTSD measured by paper and pencil instruments. War zone troops complained more often of somatic

discomfort than did non war zone troops, citing headaches (22% versus 13%), general aches and pains (20% versus 13%), lack of energy (18% versus 12%), sleep disturbances (17% versus 10%), and common cold or flu (16% versus 11 %).
Troops who served in the Persian Gulf described more mental health symptoms as war zone stress severity increased, and symptom expression among 349 war zone troops increased over a 1 year follow up interval on measures of depression, anxiety, anger, physical distress symptoms, and PTSD. Among those who served in the Persian Gulf war zone, ethnic minority troops were more frequently assigned PTSD diagnoses than were their white counterparts; however, women did not evidence greater vulnerability to negative psychological sequelae to war zone exposure than men. War zone related PTSD diagnoses were associated with low levels of the personality hardiness dimension of commitment, reliance on avoidance as a coping mechanism, low perceived family cohesion, and low satisfaction with available social supports.
Comprehensive structured clinical diagnostic interviews were administered to a subset of troops judged to be at high risk for negative psychological outcomes to war zone trauma by virtue of particularly gruesome war-zone assignments, i.e., graves registration or body handling duties, during the Persian Gulf War. Among 24 Louisiana based troops of the 630th Quartermaster Company who performed Persian Gulf graves registration duties, prevalence of current PTSD was found to be 46%, and rates of comorbid disorders among troops assigned PTSD diagnoses included major depression (55%), alcohol abuse/dependence (27%), depressive disorder NOS (18%), and simple phobia (9%). Findings were replicated and extended by assessments conducted among the Puerto Rico based 246th Quartermaster Battalion with subsequent comparisons of 40 troops who performed graves registration duties in the Persian Gulf to 20 similarly trained troops who were not deployed to the Persian Gulf and who had no ODS graves registration exposure. Diagnoses of current PTSD were found in 48% of war zone deployed troops; whereas, none of the non war zone deployed troops met PTSD criteria. Low rates of pre-ODS deployment psychiatric disorders were found in both subsets of troops. Current comorbid diagnoses among troops who met criteria for PTSD included depressive disorder (37%), alcohol dependence (21 %), other anxiety disorder (5%), and polysubstance dependence (5%). One year follow-up assessments were completed with 17 troops of the 630th Quartermaster Company who were assigned Persian Gulf graves registration duties, and 47% met criteria for current PTSD. Of the 26 troops of the 246th Quartermaster Battalion who performed war zone graves registration duties and completed follow up assessment, 38% evidenced current PTSD. Thus, 42% of troops assessed at follow up were classified as positive for PTSD two years after war zone service.

PUBLICATIONS

Sutker PB, Uddo M, Brailey K, Allain AN. War-zone trauma and stress-related symptoms in Operation Desert Storm/Shield (ODS) returnees. Journal of Social Issues, 49(4), 33-49, 1993.

Sutker P, Uddo M, Brailey K, Allain A, Errera P. Psychological symptoms and psychiatric diagnoses in Operation Desert Storm troops serving graves registration duty. Journal of Traumatic Stress, 7, 159-171, 1994.

Sutker P, Uddo M, Brailey K, Vasterling J. Psychopathology in war-zone deployed and nondeployed Operation Desert Storm troops assigned graves registration duties. Journal of Abnormal Psychology, 103 (2), 383-390. 1994.

Title Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC Pittsburgh

Study Start Date 4/1/94

Estimated Completion Date 3/31/95

Project Status Complete

VA-13

Summary

OVERALL PROJECT OBJECTIVE: To collect data on a sample of 50 Persian Gulf Veterans who have returned with physical or psychosocial complaints.
SPECIFIC AIMS: To obtain pilot data to gain objective evidence of impairment of cognitive ability and brain function, or of psychosocial disability.
METHODOLOGY: Subjects were tested in our laboratories with an extensive battery of neuropsychological tests, event-related brain potentials, measures of cardiac and pupillary reactivity, laboratory measures of attention, and various interviews, tests, and questionnaires to evaluate psychosocial status with an emphasis of PTSD. Data were analyzed descriptively and in reference to available literature and normative information. The presence of abnormal findings should provide the basis for further study with a controlled investigation.
EXPECTED PRODUCTS: To obtain neuropsychological, psychophysiological and psychosocial data from 50 Persian Gulf veterans.
STATUS RESULTS TO DATE: A paper describing the neuropsychological test results has been accepted for publication in the Journal of the International Neuropsychological Society. The findings are summarized as follows. A neuropsychological investigation of 21 Persian Gulf veterans and 38 demographically matched controls was conducted in order to make a preliminary determination concerning presence of neuropsychlogical deficits associated with the Persian Gulf War experience. The neuropsychological test battery consisted of measures of complex attention, memory, and motor skills, previously shown to be sensitive to exposure to environmental toxins. It was found that the Persian Gulf veterans group did not demonstrate substantial impairment, but an impairment index derived from 14 test variables was statistically significantly different from controls in the direction of poorer performance. A second study involving the psychophysiological data is currently being prepared for submission to Biological Psychiatry as a brief report. We found prolonged latencies, without reduction in amplitude, in the P300 component of the auditory event related potential (ERP) in the Persian Gulf veterans. This prolongation was significantly different from demographically matched controls when we only considered the 13 of 19 subjects who had complaints related to cognitive function, such as memory impairment. The remaining 6 subjects had normal latencies. Prior research has shown that increased latencies are associated with decline in cognitive efficiency. We therefore concluded that reported cognitive deficits may not be associated with psychological distress alone.

PUBLICATIONS

Goldstein G, Beers SR, Morrow L A, Shemansky WJ, Steinhauer SR. A preliminary neuropsychological study of Persian Gulf veterans. Journal of the International Neuropsychological Society. (In press).

Title Vaccine-Mediated Immunity Against Leishmaniasis

Research Focus: Leishmaniasis
Research Type: Basic Research
Agency VA
Study Location VAMC Cleveland
Study Start Date 1/1/93
Estimated Completion Date 9/30/99
Project Status Ongoing
VA-15

Summary

OVERALL PROJECT OBJECTIVE: Vaccine design, with a focus on the use of adjuvants and antigen delivery systems to induce specific T cell responses.
SPECIFIC AIMS: 1. Investigate how different routes of antigen delivery induce different T cell responses; 2. Optimize protective Th1 cell respones to vaccine by manipulation of the in vivo lymphokine environment; 3. Examine the role of accessory cells in lymphocyte activation by targeting recombinant antigen to different classes of APC; 4. Develop vaccination protocols that selectively target antigen to MHC I for optimal activation of CD8+ T cells.
METHODOLOGY: A mouse model of leishmaniasis was used (L. major). Both soluble promastigote antigen and recombinant gp63, LACK, and PSA-2 antigens are employed as vaccine immunogens. Current studies are focusing on the use of recombinant interleukin-12 as a vaccine adjuvant and on the use of DNA vaccine techniques. Outcomes to be tested include assessment of whether vaccinated animals are resistant or susceptible to challenge infection and detailed analysis of the T cell phenotype resulting from vaccination. This includes in vivo RNA analysis and ex vivo cytokine production and ELISA assay. The PSA-2 antigen was cloned, sequenced and is being altered by fusion PCR to generate chimeric proteins with functional cytokine and antigen activities.
DNA vaccination is being addressed using plasmids that express vaccine antigen with or without IL-2, IL-12, CD40, or B7 costimulatory signals.
EXPECTED PRODUCTS (MILESTONES): We have developed a recombinant PSA-2 antigen for vaccination and are generating recombinant cytokine/antigen fusion proteins for delivery of immunogen and adjuvant in a single molecule.
STATUS/RESULTS TO DATE: Ongoing. Recombinant IL-12 is an effective vaccine adjuvant and overcomes host-defined predispositions towards nonprotective Th2 CD4+ T cell responses. Considerable work on the basic immunology of IL-12 in the murine leishmaniasis model was necessary before pursuing the vaccine-related goals of this grant and these studies generated the bulk of the publications to date.

PUBLICATIONS

Heinzel FP, Rerko RM, Ling P, Hakimi J, Schoenhaut DS. 1994. Interleukin 12 is produced in vivo during endotoxemia and stimulates synthesis of interferon-g. Infect. Immun. 62:4244-9.

Heinzel FP. 1994. Interleukin 12 and the regulation of CD4+ T cell subset responses during murine leishmaniasis. Parasitol. Today. 10:190-2.

Heinzel FP, Schoenhaut D, Rerko R, Roesser L, Gately M. 1993. Recombinant murine IL-12 cures infection with Leishmania major in susceptible mice. J. Exp. Med. 177:1505-1509.

Title Protective Immunity in Experimental Visceral Leishmaniasis

Research Focus: Leishmaniasis
Research Type: Basic Research
Agency VA
Study Location VAMC San Antonio
Study Start Date 10/1/94
Estimated Completion Date 9/30/97
Project Status Ongoing
VA-16

Summary

OVERALL PROJECT OBJECTIVE: Characterization of the protective immune mechanisms in experimental visceral leishmania, and identification of the parasite antigens which client such protective responses.
SPECIFIC AIMS: Studies of the murine model of visceral leishmaniasis will provide a means to characterize the operative protective immune mechanisms as well as identify parasite antigens which have potential use for human vaccination. Characterization of the protective immune mechanisms in experimental visceral leishmaniasis will be accomplished by studies of the in situ cytokine response to primary infection in susceptible mice, as well as identification of responses associated with the acquisation of immunity. Once the the mechanisms associated with protective immunity have been defined the parasite antigens relevant to immunity can be identified. Purified and recombinant Leishmania donovani antigens which elicit an in vitro cytokine response which correlates with in vivo immunity will be identified and characterized.
METHODOLOGY: The murine model of visceral leishmaniasis will be used to characterize the mechanisms involved in protective immunity at the tissue level. These studies will be performed using a reverse transcriptase polymerase chain reaction methodology for measuring cytokine (IL 4, 11 6, IL 10, IL12, IFN @, TNF a, and TGF @) gene expression in skin, lymph node, and spleen. Comparisons will be made between naive (susceptible) and immunized (resistant) mice. Once the in situ mechanisms are better defined, in vitro correlates of immunity (e.g. a certain cytokine profile) can be identified. Semipurified or purified soluble antigens will then be tested in vitro for their capacity to elicit a proliferative response and protective cytokine profile in stimulate splenocytes or lymph nodes. A recombinant library will also be directly screened using spleen cells from immune animals. This will enable the identification of vaccine candidates which can subsequently tested in the animal model.
EXPECTED PRODUCTS (MILESTONES):
1. Identification of cytokines associated with control of infection
2. Identification of cytokines associated with resistance to re infection
3. Identification of antigens having the potential to stimulate protective immunity
STATUS/RESULTS TO DATE: Mice infected with L. donovani amastigotes by the intradermal route develop minimal curaneous swelling, regional lymphadenopathy, but no detectable visceral (hepatic) parasite burden. In contrast, mice infected by the intravenous route develop progressive hepatosplenomegaly and a visceral parasite burden that increases up to 4-6 weeks after infection. To understand the mechanisms associated with the local control of infection we have characterized the in situ expression of cytokines (IFN-g, IL-4, IL-10, and IL-12) in the spleen, draining lymph node, and cutaneous site of inoculation using quantitative reverse transcriptase-polymerase chain reaction methods. There appears to be considerably greater expression of IFN-g and IL-12p40 in the draining lymph node following cutaneous inoculation compared to the spleen, but was greater in LN. There was significant expression of both IL-10 and IL-12 at the cutaneous site of inoculation starting 7 days after infection. Thus there seems to be a mixed Th1/Th2 type response to primary infection in this model, but local control (skin and draining LN) appears to be associated with markedly increased levels of IFN-g and IL-12 RNA. These differences may be due to more efficient antigen presenation at the LN level following cutaneous infection (possibly from migration of cutaneous Langerhans cells), or the induction of immunological tolerance following intravenous infection. Studies to further define the mechanisms involved are in the progress.

PUBLICATIONS none to date

(blank)

Title Immunological Evaluation of Persian Gulf Veterans

Research Focus: Immunology
Research Type: Clinical Epidemiology Research
Agency VA
Study Location VAMC Birmingham
Study Start Date 4/1/94
Estimated Completion Date 5/1/95
Project Status Complete
VA-17

Summary

OVERALL PROJECT OBJECTIVE: To understand possible contributions of immunological abnormalities to disease manifestations in Persian Gulf War veterans. The chief complaints of these veterans include arthralgias and central nervous system dysfunctions, i.e., disorders which may have a common immunological basis. The intent of this proposal is to expand upon ongoing medical and neurobehavioral analyses of veterans from the Birmingham VA Medical Center to include an immunologic component in the evaluation of these veterans.
SPECIFIC AIMS: Evaluate potential changes in the immunological status of Persian Gulf War veterans using sensitive biological assays of immune cellular function such as those previously described for use in evaluating chemical sensitivities.
METHODOLOGY: Functional immune integrity of peripheral blood mononuclear cells was tested in subjects (approximately 50) and age- and sex-matched controls (approximately 10). Longitudinal samples were obtained from 2 subjects. Antigenic and mitogenic responses were determined using the recall antigen tetanus toxoid and the T-cell mitogen phytohemagglutinin. Proliferative responses were measured by tritiated thymidine uptake and compared with cultures of unstimulated subject or control cells. Data were reduced and statistically compared using a two-sample, unpaired t test.
STATUS/RESULTS TO DATE: The final number of samples analyzed for immune function in mitogen-induced and antigen-induced proliferative assays included approximately 40 Persian Gulf veterans and 7 age- and sex-matched controls. When these two groups were compared for mitogenic responses, no significant difference was noted ($p > 0.06$). This finding suggested that the subjects and controls had similar T cell function potential since the phytohemagglutinin mitogen is a polyclonal stimulant used to assess potential for T cell responses. However, when these two groups were compared for antigenic response using the tetanus toxoid recall antigen, a significant difference was noted ($p = 0.027$). With less than 50 subjects and less than 10 - 15 controls, these data are to be viewed and interpreted only as preliminary findings suggestive of a difference in recall response to antigenic stimulation. More subjects are needed prior to publication or dissemination of these preliminary findings.

PUBLICATIONS none to date

Title Chronic Gastrointestinal Illness in Persian Gulf Veterans

Research Focus: Miscellaneous **Research Type:** Clinical Epidemiology Research

Agency VA **Study Location** VAMC Boston

Study Start Date 10/1/94 **Estimated Completion Date** 10/1/96

Project Status Ongoing VA-18

Summary

OVERALL PROJECT OBJECTIVE: Clearly define the most prevalent chronic gastrointestinal symptoms in a unit of Persian Gulf veterans.
SPECIFIC AIMS: 1. Determine and define symptom complex. 2. Look for underlying pathophysiology.
METHODOLOGY: Survey of a single unit of Persian Gulf veterans. Hydrogen breath tests on affected individuals.
EXPECTED PRODUCTS (MILESTONES): Ultimately to identify pathophysiology of the gastrointestinal symptoms.
STATUS/RESULTS TO DATE: Survey completed. Have identified most prevalent symptoms.
Note: Following is quoted from poster accepted for Poster Presentation at Digestive Disease week in San Diego, May 1995, Chronic Gastrointestinal Symptoms In Persian Gulf Veterans; MB Sostek, S Jackson, JK Linevsky, EM Schimmel, BG Fincke; Departments of Medicine and Social Services, Boston Veterans Affairs Medical Center and Boston University School of Medicine, Boston, MA.
Background: Persian Gulf Syndrome is characterized by a constellation of chronic symptoms postdating deployment to the Gulf Region in 1991. Intermittent diarrhea is one of the eight most commonly reported symptoms. The prevalence of non-diarrheal gastrointestinal (GI) symptoms is not well documented. Over the past year, we have recieved increasing referrals for evaluation of Persian Gulf vetrans (PGV) with various GI complaints. The aims of this study were I) to determine the prevalence and spectrum of GI complaints in a representative sample from this population and II) to compare this data to a control group of soldiers not deployed to the gulf region.
Methods: A 4-page questionnaire was mailed to the 92 members of a National Guard Unit deployed to the Persian Gulf Region in 1991 and distributed to 44 members (controls) of the same unit who were not deployed to the Gulf Region in 1991. The questionnaire asked the veterans to grade current severity of 26 GI and 10 non-GI symptoms. The survey also asked veterans to recall occurrence of 5 GI symptoms either during or before the Dessert Storm mission.
Results: 57/92 Persian Gulf veterans (62%) responded to the survey. All 44 of the controls returned the suvey. The table below summarized the reported frequency of several GI symptoms in this population:

GI Symptom	Before ODS	After ODS	Controls (Current)
Loose Stool	2/57 (3%)	39/57 (68%)*	4/44(9%)
Abdominal Pain	2/57 (3%)	32/57 (56)*	3/44 (7%)
Excessive Gas	5/57 (9%)	42/57 (74%)*	10/44 (23%)
Nausea/Vomiting	2/57(3%)	13/57 (23%)	1/44 (2%)
Hematochezia	no data	4/57 (7%)	0/44 (0%)

*p<.0001 compared to symptome frequency before desert storm.
Additional frequently reported GI symptoms among PGV's in this survey include: sensation of incomplete rectal evacuation post defecation 34/57 (60%), and watery bowel movements following episodes of abdominal pain 30/57 (53%). The most frequent non-GI symptoms were: fatique 46/57 (81%), joint pains 42/57 (74%) and headache 38/57 (675).
Conclusion: A significant number of veterans from a single National Guard unit, deployed to the Persian Gulf, developed GI symptoms while in that region. The majority of these veterans currently continue to report persistent loose stools, lower abdominal pain, excessive gas and tenesmus. Veterans in the same unit, who were not deployed to the Gulf region, report significantly fewer chronic GI symptoms at the present time. While these symptoms are suggestive of the

development of irritable bowel syndrome following Persian Gulf deployment, further studies are needed to better understand the pathophysiology of this combination of chronic GI symptoms.

PUBLICATIONS Abstract accepted for Poster Presentation at Digestive Disease week in San Diego, May 1995.

Sostek M. High prevalence of chronic gastrointestinal symptoms in a national guard unit of Persian Gulf veterans. Accepted to the Am J of Gastroent. Dec. 1996

Title Psychological Adjustment in Operation Desert Shield/Storm Veterans

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC Gainesville

Study Start Date 7/1/91

Estimated Completion Date 7/1/93

Project Status Complete

VA-20

Summary

OVERALL PROJECT OBJECTIVE: The study examined the psychological effects of military service in the Persian Gulf during Operation Desert Shield/Storm.
SPECIFIC AIMS: Noncombat reserve and national guard troops who were in the Persian Gulf were compared to activated and nonactivated troops who remained in the United States during the Persian Gulf War. The study determined the difference between the three groups in terms of psychological adjustment and impact on cognitions and feelings about the war.
METHODOLOGY: Subjects were 507 members of National Guard and Reserve units in Northcentral Florida. Data was collected over a two-month time period from July 29 to September 23, 1991. Thus, the data was collected approximately 6 months after the ground war ended, and usually from one to two months after the troops had returned to the United States. Data was collected during the customary monthly weekend drills, and with the endorsement of the units' commanders. For units that had been deployed to the Persian Gulf, troops were also briefed about the potential emotional and family problems associated with post-war adjustment, were provided with information about veterans benefits, and were advised of the availability of readjustment counseling in our VAMC and other facilities in their communities. The order of presentation of these elements of necessity varied from site to site, and sometimes within a site, as it was imperative to oblige the needs of the units' and those of others involved (e.g. Vet Center counselors, veterans benefits counselors).
Subjects were assured of the anonymity of their responses, and were instructed to hand their packets of questionnaires directly to the study's investigators, in an attempt to assuage subjects' concerns that their careers might be jeopardized by their disclosures. However, it is evident that doubts lingered, as some subjects commented on their concerns about how the results might be used, and many failed to provide their names (requested in order to conduct follow-up). Six troops omitted information about their gender as well, and were thus excluded from analysis.
The subjects, tested at different sites, consisted entirely of combat support troops, including engineering units, mobile medical units, transportation units, military police, a quartermaster unit, and a demolition unit. Of the 507 troops included as subjects, 397 were male and 110 were female. Although a minority in the other units, females made up about 50% of the mobile medical units. For the purpose of analysis, subjects are categorized as deployed (i.e. activated and sent to the Persian Gulf during Operation Desert Storm/Shield), activated/not deployed (activated for duty during Operation Desert Storm/Shield but serving in the United States) and not activated (remaining on non-active status throughout Operation Desert Storm/Shield).

	Males	Females
Deployed	213	75
Not Activated	173	26
Activated/Not Deployed	11	9

Due to the low numbers currently available in the Activated/Not Deployed category, the analysis is restricted to Deployed and Not Activated.
Unit officers provided strong encouragement to their troops to participate in the study, and although it is not possible to know exactly what percentage did actually participate, 90% would be a reasonable estimate. Of those subjects that did return their questionnaire packets, many did not complete the entire protocol, which normally required about one hour to complete. The questionnaires were presented in the following order: 1) demographic questionnaire, 2) combat

exposure scale from the War Stress Interview, 3) SCL-90 plus 15 additional items from the Cincinnati Stress Reaction Scales, 4) Gainesville Readjustment Questionnaire, 5) Family Environment Scale, 6) Impact of Events Scale, 7) Work Environment Scale.
RESULTS: Analysis of the data indicated that individuals deployed to the Persian Gulf differed significantly from individuals in reserve and guard units who were not activated during ODS. Specifically, they reported a greater degree of intrusion and avoidance symptoms related to the war, as measured by the IES. ODS veterans who were also veterans of prior wars reported fewer intrusion and avoidance symptoms. Age was not found to be a significant factor. The scores on the Gainesville Questionnaire, postulated to indicate enhanced coping strategies, did not correlate significantly with evidence of superior mental health on the SCL-90-R or the IES. A lack of significant difference between ODS veterans and control group in terms of SCL-90-R scores suggests that the overall psychological health of most of the ODS veterans does not appear to have been affected by the war. However, it is apparent that some subjects had lingering doubts about the possible repercussions of admitting problems, and this is likely to have suppressed some of the SCL-90-R scores, which showed less pathology than non-patient norms in the general population. Additionally, the units available to this investigation were all combat support units, and combat exposure was consequently more limited and less severe than for combat units. Only 156 subjects returned follow-up data, with only 27 completing all 3 follow-ups. An ANOVA conducted to determine if the follow-up group was representative of the larger population resulted in a significant interaction effect, in which ODS veterans who cooperated with the follow-up admitting to higher intrusion and avoidance symptoms on their initial testing. Thus, the follow-up data was concluded to not represent a random sample of the desired population. One subject found the mailed follow-up questionnaires caused discomfort and indicated that she did not want to be contacted further. We abided by her request. No other adverse effects were noted.

PUBLICATIONS Returning Persian Gulf Troops: First Year Findings, published by Northeast Program Evaluation Center (NEPEC), VAMC, West Haven, Connecticut, 1992.

Title A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS

Research Focus: Brain & Nervous System

Research Type: Clinical Epidemiology Research

Agency VA

Study Location VAMC Phoenix

Study Start Date 1/8/92

Estimated Completion Date 12/3/94

Project Status Complete

VA-21

Summary

OVERALL PROJECT OBJECTIVE: The objective of the study was to compare three Arizona Reserve Medical Units involved in Operation Desert Storm on PTSD symptomatology one year after the war utilizing the revised Mississippi Scale for Combat-Related PTSD (Keane, Caddell, and Taylor, 1988). One of the groups was deployed to Saudi Arabia(N=42), one to England (N=37), and one to Arizona (N=17).
SPECIFIC AIMS: The hypothesis was that the group deployed to Saudi Arabia would have significantly higher scores than the other two groups.
METHODOLOGY: Subjects consisted of three Arizona Military Reserve Medical Units, one deployed to Saudi Arabia, one deployed to England and one deployed locally. Members of all units included physicians, nurses and other medical specialists.
The group deployed to Arizona (AZ) consisted of 17 subjects, 10 females (58.8%) and 7 males (41.2%). Of the 13 subjects in AZ who provided demographic data, 2 were age 20-29 (15.4%), 5 were 30 to 39 (38.5%), and 6 were 40 to 50 (46.2%). Ages ranged from 20 to 54. The mean age was 38.9. Mean age for females was 34.7. Mean age for males was 43.1.
The group deployed to England (ENG) consisted of 37 subjects, 21 females (56.8%) and 16 males (43.2%). Eleven were age 20-29 (29.7%), 14 were 30 to 39 (37.8%), 9 were 40 to 49 (24.3%), and 1 was 50 to 59 (2.7%). Ages ranged from 21 to 56. The mean age was 33.7. Mean age for females was 34.4. Mean age for males was 33.
The group deployed to Saudi Arabia (SA) consisted of 42 subjects, 20 females (47.6%) and 22 males (52.4%). Twelve subjects were age 20-29 (28.6%), 10 were 30-39 (23.8%), 15 were 40-50 (35.7%) and 5 were 50-59 (11.9%). Ages ranged from 21 to 56. The mean age was 37. Mean age for females was 35.8. Mean age for males was 38.1. Design, Procedures, and Instruments. These data were collected in the first half of 1992, approximately one year after the end of the Persian Gulf War. At a regular monthly unit meeting, consenting subjects were administered the current revision of the Mississippi Scale for Combat-Related PTSD (Keane, Caddell and Taylor, 1988) and a questionnaire on demographics, substance abuse and effects on family. The validity and reliability of the Mississippi Scale have been established by Keane, Caddell and Taylor (1988). Subjects were invited to write additional comments about the impact of the war and were given an opportunity to volunteer to be interviewed.
The purpose and procedures of the study were described to subjects, and they were informed that they could withdraw from the study at any time prior to publication. They were also informed that participation or refusal to participate will not affect their military careers or subsequent benefits. All responses remained confidential. Data were identified by codes rather than names.
Mississippi Scale means of the three groups were analyzed by a one-way Analysis of Variance. The Scheffe Test of Multiple Comparisons was performed post hoc. Subjects' written comments, as well as responses regarding drug and alcohol use, were compiled and summarized but not statistically analyzed. The Semi-Structured Initial Interview for Desert Storm War-Zone Personnel (Litz, Knight, Wolfe, Kaloupeck, Quinn, Krinsley, Fisher, Weathers, & Keane, 1991) was administered to ten members of SA by one of the authors. The authors analyzed the data for common themes. Interviewees' descriptions of war-zone stressors are reported in the results section of the paper.
Table 1
Demographics of Interviewees (N=10)

Variable	Males (N=3)	Females (N=7)
Mean age	48.6	39.9
Age range	45-52	22-50
Marital status		
Married	3	4
Single	--	3
Military rank		
Officer	2	5
Enlisted	1	2
Education		
Doctorate	1	--
Masters	--	2
Bachelors	--	2
Some college	2	3
Race		
Caucasian	3	7

RESULTS: Analysis of Mississippi Scale Scores

A one-way Analysis of Variance revealed a significant difference in Mississippi Scale scores among the three groups ($p < .001$). Post hoc analyses revealed that the mean score of the unit deployed to Saudi Arabia (SA) ($M = 83.98$) was significantly higher than that of the unit deployed to England (ENG) ($M = 73.61$) and the unit deployed to Arizona (AZ) ($M = 73.61$), $F(2, 103) = 9.83$, $p < .001$). Also, ENG obtained significantly higher scores than AZ. Means, standard deviations and test results are presented in Tables 3, 4 and 5.

Table 3: Means and Standard Deviations

	Mean	SD	N
SA	83.97	19.58	43
ENG	73.6	15.88	38
AZ	66.00	11.43	25

Table 4: Analysis of Variance

Effect	SS	df	MS	F	p
VAR1	5453.91	2	2726.954	9.83	.001
Within	28570.06	103	277.379	--	--

Table 5: Post hoc Comparison: Scheffe Test: p-levels marginal means for indep. var.

		AZ	ENG	SA
mean=66.00 level code:	AZ	X	0.178	0.00
mean=73.61 level code:	ENG	0.178	X	0.04
mean=83.98 level code:	SA	0.00	0.04	X

Six SA subjects (14%) scored greater than 107, the cutoff score for the diagnosis of PTSD. One of those subjects wrote on the questionnaire that he believed that his distress was caused by his Vietnam experience rather than his ODS experience. One subject in ENG scored over 107 (2.7%).

War-Zone Stressors of SA as Described by Interviewees. The unit arrived in Dhahran, Saudi Arabia, on January 4, 1991 and was evacuated on April 4, 1991. Initially billeted in Al Khobar, near the Dhahran Air Base, they were in Al Khobar when the SCUD missile hit. As medical personnel, they were not allowed to carry weapons according to the Geneva Convention, but they were required to pull guard duty both in Dhahran and in the field. They were responsible for setting up their own combat support hospital 10 miles north of the Iraqi border. The closest support hospital to the front lines, they were married with a helicopter unit and received 32% of the war's casualties from both Allied and Iraqi forces. Specific casualties were seen as especially stressful: The first female casualty, abandoned Iraqi children for whom they had no pediatric instruments, and a nurse and physician who were killed when the Claymore mines they had gathered as souvenirs exploded. Nine subjects feared for their lives. Seven said the SCUD missile landing was highly stressful. Two women found the casualties, particularly women and children, extremely stressful. Others said the

casualties were not particularly stressful because they saw severe injuries in their daily work.
Noncombat War-Zone Stressors. All subjects said that they were anxious and/or bored waiting for war to begin. Worries included fear of dying, chemical warfare, the morality of the war, and welfare of family members at home or serving in Saudi Arabia. Six subjects mentioned cultural or environmental stressors. A Jewish man feared torture if taken prisoner. Two women said Saudi men touched them and/or made sexual comments. A woman feared "crazy" Saudi drivers. Two women and two men spoke of heat and the "endless" and "dark" desert. Other stressors were relationships with other unit members, distrust of leaders, poor sanitation, and physical labor.
Deployment and Homecoming Stressors. Deployment stressors included anxiety about leaving family members and disruption of careers. Three women mentioned leaving children as the hardest thing they had ever done. One woman worried about her aging mother. Homecoming stressors included physical problems and changes in relationships and careers. Three women said that readjustment was more difficult than they had anticipated. A man divorced after the war. A woman had to start over in school. One woman attributed symptoms of diarrhea, fatigue, and irritability to a "parasite". Another had carpel tunnel. All subjects denied exacerbation of previous traumas.
Coping Strategies. Subjects coped with stress by talking to friends, relying on religious faith, reading, calling or writing home, self-talk (e.g., "Calm down." "It will be all right."), playing cards, keeping busy/exercise/physical labor, shopping, joking, eating, writing a journal, remembering home, and romance.
Several subjects compared coping strategies of men and women. One woman said that women were supportive of one another and thus had fewer emotional problems than men. Another woman said women talked easily and could cry. She said, " Maybe it seems like you're hysterical, but then you feel better. You get hugged when you cry." She said women negotiated assignments if they didn't get along with tentmates; men accepted assignments they didn't like. She noted that both soldiers who were evacuated were men. A man stated that men "adjusted better" while the women "complained about access to phones and filth and not getting mail. The older the nurse, the more bitching."
Some interviewees compared coping strategies of younger soldiers and older soldiers. Three women in their forties and a 49 year old man stated that younger soldiers had more trouble coping than older ones. Older soldiers "laughed a lot, read a lot, played bridge, [and] didn't dwell on" troubles. The man and two of the women said the younger members engaged in sex to cope with stress. One woman noticed that younger soldiers who coped best kept active. Two women noted that some unit members drank alcohol to cope.
Lasting Psychological Impact of the War. Positive effects of the war included greater faith in self, lasting friends, pride in accomplishments, adventure, and a greater sense of purpose.
Only one subject approached full PTSD. She had a flashback while working in the emergency room and still reacted to loud noises. One man said he had not slept through the night since the war. One woman was emotionally numb. One man was avoidant.
Several interviewees thought that members most affected by the war had quit the Reserves. Several thought that people who had served in Vietnam were more distressed by ODS than other members. A nurse who served in both wars said that better facilities made Vietnam "easier"; "primitive" conditions made ODS very stressful.

Common Themes of Structured Interviews (N=10)

Stressor	Number of Subjects	Women	Men
Afraid of dying	10 (100%)	7	3
SCUD landing	7 (70%)	5	2
Seeing severe casualties	2 (20%)	2	0
Waiting for war to begin	10 (100%)	7	3
Cultural/Environmental factors	6 (60%)	3	3
Interpersonal relations	3 (30%)	1	2
Distrust of leaders	3 (30%)	2	1
Hard physical labor	2 (20%)	1	1
Poor sanitation	3 (30%)	3	1

Leaving children	3 (30%)	3	0
Leaving other family members	1 (10%)	1	0
Relationship and/or career disruption	5 (50%)	4	1
War-related physical problems	2 (20%)	2	0
Coping Strategies			
Talking to friends	6 (60%)	4	2
Religion	4 (40%)	3	1
Reading	4 (40%)	2	2
Calling/Writing home	3 (30%)	2	1
Exercise/Physical Labor	3 (30%)	2	1
Self-talk (e.g., "calm down", "I'm all right")	3 (30%)	3	0
Shopping	2 (20%)	1	1
Joking	2 (20%)	1	1
Eating	1 (20%)	1	1
Writing a journal	1 (10%)	1	0
Remembering home	1 (10%)	0	1
Romance	1 (10%)	0	1
Lasting Psychological Impact (At the time of the study)			
Positive effects	6 (60%)	5	1
Confidence/Pride/Purpose	4 (40%)	3	1
Lasting friends	3 (30%)	2	1
Adventure	2 (20%)	1	1
PTSD Symptoms	4 (40%)	2	2
Intrusive thoughts	1 (10%)	1	--
Startle response	1 (10%)	1	--
Sleep disturbance	1 (10%)	--	1
Emotional numbing	1 (10%)	1	--
Flashbacks	1 (10%)	1	--
Avoidance	1 (10%)	--	1

PUBLICATIONS none to date

Title Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans

Research Focus: Brain & Nervous System

Research Type: Epidemiology Research

Agency VA

Study Location VAMC Boston

Study Start Date 9/11/95

Estimated Completion Date 3/19/98

Project Status Ongoing

VA-30

Summary

OVERALL PROJECT OBJECTIVE: The primary objective of this study is to identify and describe the effects of potential predictors on the functional health status and health perceptions of male and female veterans approximately four years after their deployment to the Persian Gulf; and to examine if and how identified risk factors differ between female and male veterans. A secondary objective of the proposed project is to ascertain the prevalence of multiple chemical sensitivity (MCS)-like symptoms reported among this population, and to explore risk factors for the development of this syndrome.

SPECIFIC AIMS: The more specific goal of this study is to use the obtained data to significantly advance DoD screening and intervention efforts aimed at enhancing positive military and post-deployment adaptation among soldiers, especially women. With women's rapidly increasing representation in the U.S. Armed Forces, there is a pressing need to investigate these relationships, and to understand factors that might be distinctively associated with womens well-being, both during and following war-time deployment.

METHODOLOGY: By using cross-sectional and longitudinal data from an existing, carefully followed military cohort and by expanding predefined measures of health symptoms, and health perceptions, this investigation is conducting analyses that focus directly on: (a) defining the set of reported environmental and psychosocial combat-theater exposures and physical health variables associated with female and male soldiers recent deployment; and, (b) describing the relationship of these variables to functional status and self-reported physical health. A primary emphasis is on investigating the role or impact of gender, specifically, whether female gender is a significant factor in predicting either functional health status or health perceptions. Data analyses will proceed through a series of three major stages. The initial stage involves generation of descriptive analyses for all variables of interest and will permit comparison of responses between women and men. The second stage involves the determination of bivariate odds ratios of gender, PTSD diagnostic status, and environmental exposure on functional health status. The third stage involves multivariate regression procedures to examine the effects of gender, PTSD and reported environmental exposure on functional status and on self-reported health.

In addition, an exploratory analysis will be conducted of the comprehensive symptom review results with respect to the diagnosis of Multiple Chemical Sensitivity. One of the first steps in ascertaining the prevalence of MCS-like symptoms among our study population is developing a survey instrument that can be used to identify subjects with MCS-like symptoms. To date, there is only one survey instrument that has been validated to assess MCS symptoms. However, due to its length, we are currently testing the validity of a shortened version of this existing questionnaire on patients referred to the Massachusetts Respiratory Hospital, and controls recruited by participating patients. Depending on the prevalence of individuals who meet criteria for MCS-like symptoms, mulivariate models similar to those for functional status with MCS-like symptoms as the dependent variable will be conducted.

EXPECTED PRODUCTS (MILESTONES): To develop a shorter questionnaire than the one currently used to identify MCS, scientific publications on Persian Gulf War illnesses (including the impact of stress and trauma on outcome, annual reports, gender models of health outcomes.

STATUS/RESULTS TO DATE: The shortened MCS questionnaire has been distributed to subjects. The larger survey instrument is currently being piloted and will soon be mailed.

PUBLICATIONS

Proctor SP, Wolfe J, Friedman M. Evaluation of health symptoms reported by Gulf War veterans. Paper presented at the Annual Meeting of the International Society for Environmental Epidemiology, Research Triangle Park, NC. September 1994.

Wolfe J, Brown PJ, Bucsela ML. Symptom responses of female Vietnam veterans to Operation Desert Storm. American Journal of Psychiatry,149, 676-679, 1992.

Wolfe J, Brown P, Kelley J. Reassessing war stress: exposure and the Gulf War. Journal of Social Issues, 49, 15-31, 1993.

Title Stress Symptoms and Their Causal Attribution in Desert Storm Veterans

Research Focus: Brain & Nervous System

Research Type: Epidemiology Research

Agency VA

Study Location VAMC Clarksburg

Study Start Date 12/1/95

Estimated Completion Date 12/31/96

Project Status Ongoing

VA-36

Summary

OVERALL PROJECT OBJECTIVE: Describe motivational aspects of stress in relationship to war experience.
SPECIFIC AIMS: Determine stress symptoms and their causal attribution in Desert Storm veterans.
METHODOLOGY: Survey Methodology: Mail out to 200 randomly selected subjects. Expected return rate of 80%. Date analysis via multiple regression methodology.
EXPECTED PRODUCTS (MILESTONES): Pilot study - may lead to further studies.
STATUS/RESULTS TO DATE: Sample selected and results coming in. Execution has been complicated by multiple change of address situations. Subjects are being pursued, and where necessary, replacement subjects are selected. Thus far, 104 completed responses have been received.

PUBLICATIONS none to date

Title Musculoskeletal Symptoms in Gulf War Syndrome

Research Focus: Miscellaneous
Research Type: Clinical Epidemiology Research
Agency VA
Study Location VAMC Long Beach
Study Start Date 1/1/94
Estimated Completion Date 1/1/99
Project Status Ongoing
VA-40

Summary

OVERALL PROJECT OBJECTIVE: The Gulf War Syndrome is most likely a heterologous group of disorders resulting from the interaction of each veteran's host defense against the variety of environmental, viral, bacterial and stress toxins unique to the Persian Gulf War. One of the more debilitating symptoms of the GWS has been the arthralgia and arthritis. These complaints are relatively common to foreign deployments. A question arises as to whether musculoskeletal complaints are indeed a manifestation unique to Gulf War Syndrome. The project will address a fundamental question about the Gulf War Syndrome: Do the musculoskeletal symptoms in the GWS reflect those of long foreign deployment or are there unique aspects of these symptoms that identify these symptoms as part of Gulf War Syndrome.
SPECIFIC AIMS:1. Survey deployments for musculoskeletal symptoms via questionnaire; 2. Compare comparative peace-time vs. Gulf War deployments for musculoskeletal symptoms; 3. Analyze arthritis/arthralgia with comprehensive physical and laboratory examinations.
METHODOLOGY: Veterans of the Persian Gulf War with and without symptoms of the Gulf War Syndrome and healthy veterans of the same period who did not serve in the Persian Gulf but have been deployed for peaceful missions will receive a questionnaire which, if positive, will be followed by comprehensive musculoskeletal evaluation in the Department of Veterans Affairs Medical Center, Long Beach (VAMCLB) and March Air Force Base, California. Statistic analysis of the comparative features of those examinations will be evaluated for appearance of features that could be related to the other than foreign deployment, i.e., GWS.
EXPECTED PRODUCTS (MILESTONES): 1. Survey and range of musculoskeletal symptoms secondary to foreign deployments; 2. Comparison of symptoms between foreign deployments and those to GW theater; 3. Statistical analysis based on chi square and regression analysis of independent variables. Physical and laboratory examination data of deployed reservists/veterans with persistent arthritis/arthralgia complaints from GWS.
STATUS/RESULTS TO DATE: 200+ initial questionnaires; 25 comprehensive examinations. Statistical analysis ongoing.

PUBLICATIONS none to date

Title Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder

Research Focus: Miscellaneous
Research Type: Epidemiology Research
Agency VA
Study Location VAMC Gainesville
Study Start Date 11/1/95
Estimated Completion Date 6/30/96
Project Status Ongoing
VA-46

Summary

OVERALL PROJECT OBJECTIVE: To compare visceral sensation in normal subjects, patients with irritable bowel syndrome and patients with diarrhea that abruptly began while serving in the Persian Gulf.
SPECIFIC AIMS: a) To determine if Persian Gulf veterans with abdominal pain, diarrhea and bloating with a negative investigative work-up have an underlying visceral hypersensitivity or a generalized decreased pain threshold. b) To examine the heightened visceral sensitivity present in patients with irritable bowel syndrome and compare the data to those obtained for Persian Gulf veterans with diarrhea. c) To investigate whether an acute treatment with octreotide will increase the tolerance to balloon distention of the rectum and extremity immersion in ice water in Persian Gulf veterans, patients, with the irritable bowel syndrome, and controls. d) To determine the effect of octreotide on oral-cecal transit as measured by the lactulose hydrogen breath test.
METHODOLOGY: Study Design: Informed consent is being obtained prior to the start of the trial. A complete medical history and physical exam will be performed. Blood samples will be collected for a pregnancy test when appropriate. Participants will be asked to discontinue all medications for at least 24 hours before the study, to fast for 12 hours, and to take a Fleet's enema 2 hours before the test procedure. Both the ice water tolerance test and the balloon distention tolerance test will be performed in controls, patients with irritable bowel syndrome, and in Persian Gulf veterans both at baseline and after the administration of octreotide 100 mg subcutaneously. Oral-cecal Transit: The effect of octreotide on small bowel transit will be assessed by the hydrogen breath test. Lactulose (10 g) will service as the carbohydrate substrate for the breath test. Breath hydrogen concentration is measured by gas chromatography every 15 minutes until peak hydrogen excretion occurs. Peak hydrogen excretion is defined as the highest hydrogen concentration before two successive lower concentrations. Peak hydrogen excretion is the point in time at which the lactulose substrate has reach the cecum. Two points on the hydrogen curve will be used to calculate small intestinal transit. The first is the time to an initial sustained increase of hydrogen concentration of ³10 ppm over baseline. The second point is the time to peak hydrogen excretion. Ice Water Tolerance: The ice water tolerance test is performed to determine if patients have a generalized nonspecific lowered pain threshold from a central pathway. All subjects will be asked to insert their right hand into a mixture of ice and water to the wrist point and to hold it there for as long as possible. The time before withdrawing the hand from the water will be measured with a stop watch for each subject. If the hand is not withdrawn before 4 min, the subject will be instructed to withdraw the hand and a value of 240s will be assigned. Balloon Distention Tolerance: The balloon distention test evaluates a specific visceral afferent pathway as a cause of symptoms in patients with diarrhea. After each subject withdraws their hand from the ice water, a 5-min recovery period is observed. A standard anorectal manometry catheter or barostat (modified manometry balloon that measures rectal compliance) will then be inserted into the rectum of a depth of 10-15 cm. In normal subjects, progressive rectal distention initially leads to the perception of pressure, followed by fecal urgency, and then pain. The subjects' response to progressive rectal distention will be quantitated as: 1) first rectal sensation of the balloon, 2) urge to defecate from balloon distention, 3) rectal discomfort from balloon distention and, 4) rectal pain from balloon distention. The rectal balloon will then be distended in a stepwise fashion by adding 20 ml of air every 3 minutes. Unless this represents the subject's maximum tolerable volume, additional 20-ml increments of air will be added at 3-min intervals up to a maximum of 300 ml. The maximum tolerable volume will be defined as the volume at which the subject requests termination of the

procedure because of discomfort. If the subject does not report discomfort, a value of 200 ml will be assigned. After baseline measurements of ice water and balloon distention tolerance, all subjects are being brought back another day for octreotide testing. Octreotide 100 mg will be subcutaneously administered. Thirty minutes following the injection, the ice water and balloon distention tolerance will be repeated in exactly the same manner as above and compared to baseline values.

EXPECTED PRODUCTS (MILESTONES): Expected results are that the patients with Persian Gulf diarrhea, as well as irritable bowel syndrome, will have similar rectal sensation, as well as similar rectal urge to defecate, as well as similar discomfort relative to distention. Second, it is not expected that there should be a difference in ice water tolerance among either of the three groups.

STATUS/RESULTS TO DATE: At this time, 18 patients have been studied (4 normals, 5 irritable bowel syndrome patients, and 9 patients with Persian Gulf diarrhea). Patients who developed chronic diarrhea while in the Persian Gulf have a significantly lower threshold for symptoms of initial rectal sensation and the perception of discomfort with rectal balloon distension. This visceral hypersensitivity in Persian Gulf Veterans is similar to that observed in patients with Irritable Bowel Syndrome. The hydrogen breath test and octreotide protocols have not yet been completed.

PUBLICATIONS none to date

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